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ARCHIVES OF DISEASE IN CHILDHOOD.

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HUGH THURSFIELD, D.M., F.R.C.P., and REGINALD MILLER, M.D., F.R.C.P.

WITH THE HELP OF

H. C. CAMERON, M.D., F.R.C.P.
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C. MAX PAGE, D.S.O., M.S., F.R.C.S.
LEONARD G. PARSONS, M.D., F.R.C.P.
G. F. STILL, M.D., F.R.C.P.
EDITOR OF THE *British Medical Journal*.

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STUDIES IN THE ANÆMIAS OF INFANCY AND EARLY CHILDHOOD

(From the Children's Hospital and the Department of Diseases of Children of the University, Birmingham).

Part VIII.—Leukæmia (leucosis) in Children*

BY

ROBERT GITTINS, M.D., M.R.C.P., D.T.M. & H.

Leukæmia is a disease which has always held great attraction for the clinician and pathologist, for there are few diseases which can be studied with such simple apparatus and in which the results lead to such fascinating speculations on cellular development and function. Although these speculations have so far not led to success in treatment, the careful study of leukæmia has considerable practical value, not only in the sphere of differential diagnosis (for there is only a minority of blood diseases, in which the possibility of a leukæmic process has not to be excluded), but also in throwing light on processes which are later seen to possess analogous features. It is, therefore, somewhat surprising that only a relatively small number of papers have been written dealing with the aspects of leukæmia in childhood. The present paper has been written partly for this reason, and partly because when the present studies on anæmia were in progress it was found impossible adequately to deal with diseases of the erythron without considering diseases of the leucon (the leucocyte and its predecessors).

Many acute leukæmias are in greater or less degree ' aleukæmic,' and frequently present considerable difficulty in recognition and identification; yet it is almost exclusively this acute type which occurs in children, and the present series does not include a chronic case, nor has one been found in the records of the Hospital. Acute hæmolytic (erythronoclastic) anæmia, von Jaksch's anæmia, infective mononucleosis, some infective and septic conditions, and even severe nutritional anæmia may simulate leukæmia, and without hæmatological investigation, may for a time be indistinguishable from it. Too much emphasis can scarcely be laid on the acuteness of leukæmia, and the frequency of aleukæmia in children, and the consequent difficulties in hæmatological examination. Moreover, such an examination

* This communication is based on the personal study of fourteen cases, the detailed records of which have had to be omitted for reasons of space. Editors, A.D.C.

does not always reveal unequivocally the nature of the process, and the complete study must include also a histological examination. For these reasons it has been decided to include in this study only those cases which during the past three years have come to autopsy and of which the blood films and sections have been preserved for comparative examination.

Nomenclature.—The disease, which has been known for many years as leukæmia, was so christened because of the large number of leucocytes found in the blood stream. This invasion of the blood stream is accompanied by definite histological features, which typically are not reproduced by other disease processes. As leukæmia was further studied it became apparent that while the histological features remained more or less constant, increase of the total leucocytes in the peripheral blood was not an essential feature. Such a condition was labelled ' aleukæmic leukæmia,' although these cases usually showed definite qualitative changes in the leucocytes, similar to those in the leukæmic group. A few rare cases, showing the histological features, but with not even qualitative changes in the leucocytes of the peripheral blood have been claimed. The underlying process of the disease is one affecting the leucopoietic tissues, and for it leucosis is a more suitable term than leukæmia.

Leucosis may be divided into two chief forms—myelosis and lymphadenosis. We may then speak of:—

Leukæmic myelosis: myelosis, with an increase in total leucocytes which show also qualitative changes of leukæmia.

Aleucocythæmic myelosis: myelosis, without definite increase in total leucocytes, but with qualitative changes of leukæmia.

Aleukæmic myelosis: myelosis, with neither an increase in total leucocytes nor any qualitative change.

Similarly we may speak of leukæmic, aleucocythæmic and aleukæmic varieties of lymphadenosis, and possibly also of reticulo-endotheliosis.

Most of the present series of 14 cases fall into the category of aleucocythæmic lymphadenosis, although one case, which displayed equivocal signs, appeared to be an example of the rare condition of acute aleukæmic lymphadenosis; there were only two examples of myelosis.

Symptoms.—Although the maximum incidence of acute leucosis occurs in the first five years of life, Stransky[1] quotes Adler as stating that from the time of the discovery of leukæmia in 1845 to 1914 only seventeen cases in infants were reported of which, excluding cases of alleged congenital leukæmia, ten have been accepted. In our series the age varied from 10 months to 12 years. The onset is often insidious and anæmia develops; the presenting symptom in one of our cases was glandular swelling (myelosis), in another abdominal enlargement (myelosis) and in yet another jaundice. Pallor, except at the onset, is striking, and is often waxy in type. Nutrition is frequently good and wasting is not a feature. In three cases of lymphadenosis no glandular enlargement was noted either during life or at autopsy; indeed only one case showed more than slight enlargement

during life, and at autopsy the glands rarely appeared of more than normal size. Splenomegaly was present in all, but only marked in one of the cases of lymphadenosis; it was definitely greater in both the cases of myelosis. The presence of a large spleen (three or more finger-breadths below the costal margin) may be taken as a point in favour of the myeloid as against the lymphatic form. The size of the spleen has been observed to vary: notably in one instance of lymphadenosis, in which splenic thrombosis was suspected, but not found at autopsy. Hepatomegaly is variable and was clinically absent in two cases of lymphadenosis. Gingivitis, stomatitis, and enlargement of the tonsils have not been features in our series.

Hæmorrhagic retinitis of mild degree has been found in only one or two instances. Exudate was not observed, and the hæmorrhage took the form of small scattered flecks. According to Borgeson and Wagener[2] the eye-grounds have been found to be normal in leukæmia with white cells as high as 532,000 and red cells as low as 1·4 million per c.mm. Baar and Stransky[1] state that changes in the fundi may be absent, even when affection of the skin is widespread. It is curious that in a disease with such an outstanding tendency to widespread, though usually small, hæmorrhages, the retina should not be more frequently affected.

Except for petechiæ and purpura lesions of the skin have not been seen. Infiltration of the skin, sometimes seen in adults, particularly in chronic lymphadenosis, is extremely rare in childhood and in a series of one hundred cases in children Ramsay[3] recorded only one instance. The mucous membranes and submucous tissues of the mouth and pharynx may show similar changes as the skin, and extensive lesions may occur, but none were observed in our series. Infiltration may occur in the tonsils and this, if necrosis or infection supervene, may lead to confusion with anginal conditions of the throat: according to Opitz[4] such changes have been mistakenly interpreted as evidence for the infectious origin of leukæmia.

Considering the extensive changes in the marrow it is surprising that bone changes are such a rare manifestation of leukæmia in childhood. Radiograms, however, may show osteoporosis, cortical thinning, and elevation of the periosteum with layering. Karshner[5] has reported six such cases, but we have met with the condition only once, and the changes are well seen in Fig. 19 from this case. Occasionally pain in the bones may be complained of and even tenderness and swelling of the joints may occur, thus simulating acute rheumatism. In the case just referred to, lymphadenosis definitely supervened after an attack of acute rheumatism.

Fever, either continuous or intermittent, of an irregular type was usually present. In one instance the temperature reached 106°, owing to pontine infiltration[6]. Dyspnœa was present terminally in some cases.

It is only to be anticipated that a disease such as leucosis may occasionally produce rare and unusual features: thus, infiltration of different areas of the nervous system may produce various symptoms and signs. For instance, Bass[7] has recorded cases of acute leukæmia in children showing symptoms of cerebral hæmorrhage and a case simulating cerebro-spinal

meningitis; and according to Baar and Stransky, even peripheral paresis may be produced. One case in our series showed a pontine lesion, and reports of a variety of rare lesions may be found in the literature.

Course.—The course of the disease is usually short. Of our cases one lasted 19 weeks, two for 3 months and the remainder under 2 months. Reckoning the duration from the time of the first complaint, it is surprising, as several observers have noted, that the degree of enlargement of liver, spleen and lymph glands does not form a reliable guide to the rapidity of the course. It is possible, however, that these enlargements preceded the first obvious symptoms and thus the duration of such cases was actually longer. Occasionally remissions have been reported: Schirlitz[8] has recorded one in a child, aged 14, following blood transfusions, and Baar and Stransky state that regression of leukæmic symptoms has occurred in a few cases under the influence of an acute infection.

Chronic leucosis is rare in children, and, when it does occur, the condition is almost always a myelosis. Maternowska and Redlich[9] in publishing two cases of lymphatic leukæmia which they regarded as chronic, state that Berghans recorded the first case in 1926. The durations in Maternowska's and Redlich's cases were not more than eight and four months. In Opitz's series the durations of three of his seven cases of myelosis were 5, 3 and 2½ years.

Hæmatology.—The foregoing clinical manifestations may be produced in whole or in part by other pathological processes, and constitute only presumptive evidence of leukæmia, and therefore an examination of the blood is essential. As already pointed out acute leucosis is often aleucocythæmic in children, and the most common type is the lymphatic; in only one of our cases was the white count over 40,000 per c.mm., and a common figure was about 20,000. In myelosis, however, low total leucocyte counts are rare, the lowest count in Opitz's series being 15,000 per c.mm., while one of our two cases showed over 100,000, the other over 30,000 per c.mm.

Many of the cases in Ramsay's series displayed much higher white cell counts, even up to 300,000, but unfortunately autopsies on these cases were not obtained, and it is not possible to be certain of the type of leukæmia from the details given. Numerous cases of acute leukæmia in children have been recorded, in which the leucocyte count was high, running into hundreds of thousands. In fact the recognition that many cases in children are aleucocythæmic, is of comparatively recent occurrence.

Red cells.—Except in the early stages there is always a hypochromic anæmia, with a colour index which is often quite low. By the time complaint is made of the child's condition, the red cells have frequently been reduced to two millions or less per c.mm., and the hæmoglobin to 40 per cent. or less. At this time the platelets are almost invariably seriously reduced in numbers, usually to figures well under 100,000. The volume of the red cells measured by the hæmatocrit is small

(Wintrobe[10]); for instance, one case of lymphadenosis showed a volume index of the red cells of 0·74 and a saturation index of 0·96, and another (lymphadenosis) a volume index of 0·6. The normal value for these indices is unity. While aniso- and poikilo-cytosis, polychromasia, normoblasts and megaloblasts are more often found in myelosis, they are almost uniformly absent in acute lymphadenosis except in the early stages when infiltration of the marrow is commencing: a state of affairs which might be expected from our knowledge of the mode of production of the erythrocyte. In a paper on leukæmia by Hunter[11] the presence or absence of nucleated red cells was reported throughout; of the cases in which the diagnosis of leukæmia seemed most secure, the majority showed no nucleated red cells and the remainder a few only. It appears, then, that nucleated red cells are rare in acute leucosis in children, and their presence in any number should at once raise suspicion that the alleged leucotic process is actually an erythronoclastic (hæmolytic) one: a point of great importance since the latter is often amenable to treatment.

THE WHITE CELLS.—The close examination of the leucocytes is, of course, the one essential feature of the blood examination. No consideration of total numbers must outweigh the verdict on the presence or absence of great and widespread immaturity of these cells. It is still necessary to lay emphasis on this fact in regard to the lymphadenoses of children, since they are, as already emphasized, usually acute and aleucocythæmic. In lymphadenosis the proportion of lymphocytes and lymphoblasts is usually high, even up to 98·7 per cent. (Stransky[12]), and all other types of cells are absolutely reduced. One of our cases of lymphadenosis showed relatively few definite lymphoblasts, most of the cells being small lymphocytes of somewhat immature general appearance, and another case, probably the most interesting of any, appeared to be aleukæmic.

In myelosis especially, the variations in the differential count of the white cells are so wide, that hard and fast limits can scarcely be defined. Myeloblasts are rarely absent and promyelocytes and myelocytes are common. Baar and Stransky[1] state that in acute myelosis, although myeloblasts usually preponderate, cases showing chiefly myelocytes and even polymorphonuclear cells are sometimes met, and that the latter cells may show degenerative changes. Several of Opitz's cases of myelosis showed striking basophilia, even up to 11 per cent., and the eosinophils also were higher than in lymphadenosis. Three of the cases in his series were of chronic myelosis and in this condition there may be little anæmia, the platelets may be normal or even increased, and the more mature myeloid elements preponderate over myeloblasts.

It is to be noted that the monocytes are usually low in lymphadenosis and myelosis: a surprising feature in the latter group if Naegeli's view of their myeloid origin is correct.

As has been shown, the acute leucoses of children often show extremely immature non-granular cells in the peripheral blood; in the early cases these

were regarded as types of lymphocytes. Naegeli, however, showed that the precursor of the myelocytes, i.e., mother cell of the myeloid series, is a non-granular cell which he designated the myeloblast. The oxydase reaction was found to be positive in all granulocytes and some myeloblasts, though some of the latter were oxydase negative and hence regarded as the most immature myeloid cells. As a result of Naegeli's contribution on the characters of the myeloblast, there followed a tendency to regard non-granular cell leukæmias as myeloblastic, for it was argued that even oxydase negative cells were perhaps myeloblasts. However, more recently it has been realized from histological investigations that most leukæmias in children are truly lymphatic in type. The details of cytological differentiation in blood films and tissues are dealt with in a later section. Cases are sometimes encountered in which it is almost, if not quite, impossible to diagnose the type of leukæmia from an examination of blood films. Nevertheless, the histological differentiation on the basis of architecture and the cytological features of sections, is invariably clear—at least, such has been the lesson learned by the present study.

Interpretation of the blood picture.—The general features of the blood picture and the effect on the erythron may now be considered. Focal deposits of ' foreign ' cells in the marrow, such as those of lymphadenoma, chronic lymphadenosis and carcinoma, may easily give rise to large numbers of nucleated red cells in the blood stream; a picture which has been delineated by Piney and which is presumably due to irritation of the marrow. We have, then, in leucosis the possibility of the presence of abnormal cells, arising in two different ways: (1) the fundamental process (e.g. lymphadenosis), (2) irritation of normal marrow (or other tissues, such as reticulo-endothelium), leading to the emigration of immature forms (e.g. myelocytes, normoblasts or even monocytes). It is probably the operation of these two factors, which has lead to the conception of ' mixed ' leukæmias; but as will be suggested in another section, histological investigation of our cases has shown that, although the blood picture may reveal signs of immaturity of both myeloid and lymphatic series of cells, the type of the leukæmic process in the tissues is single and remarkably pure.

It appears that in the early stages of acute lymphadenosis or in subacute cases, the early infiltration of the marrow by the foreign cells may result in stimulation, with emigration into the blood stream, of immature forms of the myeloid cells and erythron. Evidence in favour of this was found in an example of lymphadenosis of three months' duration, but from the considerable enlargement of the organs judged to be of longer standing; and in another which developed under observation and was examined early in the process. However, by the time the majority of instances of lymphadenosis in children are examined, the invasion and infiltration of the marrow have proceeded far beyond the stage of irritation and no response is possible: in fact, the condition revealed is one of aplasia of the granular leucon, platelets and erythron, while the leukæmic picture becomes pure.

In myelosis there is more variability in the number of nucleated red cells in the peripheral blood. The more chronic of our two cases showed a good many normoblasts, while the acute one did not. It appears that in the more acute cases, where anaplasia is extreme, the formation and emigration of normoblasts is less marked.

The blood picture may be summarized as follows:—

1. Acute lymphadenosis: there is usually a moderate increase in white cells, but both high and low counts may be encountered; lymphoblasts are numerous, but occasionally only few are found; platelets are diminished when the disease is well established; there is severe anæmia in the later stages; abnormalities of the erythron are found only in the early stages; microcytosis is usual.

2. Myelosis: higher total leucocyte counts are the rule; all forms of immature myeloid cells may be present, with sometimes a high proportion of myeloblasts in the more acute types; eosinophil and basophil cells are more frequent than in lymphadenosis, and may be pronounced in chronic cases; platelets are diminished in the acute forms; anæmia is severe in the later stages; abnormalities of the erythron are more common than in lymphadenosis.

Diagnosis.—The most interesting aspect of our study of leucosis has been that concerned with diagnosis. The acute nature of the illness, the frequency of aleucocythæmic forms, the similarity of clinical features, and the occurrence of leukæmoid conditions of the blood in other diseases, frequently render the differentiation by no means easy. In this differentiation the hæmatological and histo-pathological features have to be studied intensively, and for this reason the characters of the distinctive cells, as they appear both in blood films and tissues, are described in detail later in this paper. Here only the chief conditions which may mimic leucosis are briefly dealt with.

Acute hæmolytic (erythronoclastic) anæmia.—The clinical features of the acute hæmolytic anæmia of Lederer were dealt with in Part V of this series, where it was suggested that, since the disease exerts its harmful influence not only on the mature red cell but also on its immature precursors, i.e., on the whole erythron, the term erythronoclastic would designate the anæmia better than hæmolytic. This condition may closely simulate acute leucosis; indeed, it is more than probable that the examples of recovery from acute leukæmia which occur in the literature, are in reality instances of recovery from erythronoclastic anæmia. The onset of this anæmia is usually sudden and dramatic, although, if the process is subacute, it may resemble the insidious onset of leukæmia. Typically acute erythronoclastic anæmia is a rapidly developing anæmia in a previously healthy child, and splenomegaly may develop. Lazarus[13] states that hepato- and spleno-megaly develop after remission in acute, or later, in sub-acute cases. The absence of enlarged lymph glands will not eliminate acute leucosis. Marked jaundice is not common in either, but slight icterus is more frequent in

erythronoclastic anæmia. In the early stages the blood may show a neutrophilia (twenty to forty thousand) with some immaturity of the white cells, which is of less degree than in acute myelosis: one of our cases showed 8 per cent. myelocytes, 7 per cent. immature metamyelocytes and 15 per cent. mature metamyelocytes, and Lazarus has recorded 16 per cent. myelocytes. Myeloblasts are usually absent and, in any case, scanty. The leucocytosis may, however, be extreme, and higher than found in some acute leucoses in children, e.g., 108,000 and 76,000 white cells per c.mm. (Lazarus). Sometimes, and often in subacute and chronic cases, a relative or absolute lymphocytosis may occur, which may give confusion with that of acute lymphatic leukæmia; careful examination of the lymphocytes will reveal their mature characters, as opposed to those of the lymphoblast. The colour index is often above unity and marked aniso- and poikilo-cytosis and polychromasia, many reticulocytes, normoblasts, macro-normoblasts and megaloblasts are found much more frequently in acute erythronoclastic anæmia and generally when remission, often as a result of blood transfusion, sets in; in acute lymphadenosis these are rarely seen.

ANÆMIA PSEUDOLEUKÆMICA INFANTUM (VON JAKSCH).—The disease most likely to cause confusion with leukæmia is that form of anæmia which we have described as subchronic erythronoclastic anæmia: the so-called von Jaksch's anæmia. Confusion is liable to arise on account of the immaturity of the white cells, which include a fair proportion of myelocytes and even a few myeloblasts. Lymphocytosis also may occur, and this, if marked, is differentiated from the lymphoblastosis of lymphadenosis by the mature characters of the lymphocytes. Although aniso- and poikilo-cytosis and polychromasia with an occasional normoblast may be found in acute myelosis, these features are pronounced in von Jaksch's syndrome, and normo- and megalo-blasts may reach very high numbers. Baar and Stransky[1] mention that embryonal blood-forming foci may be found in this disease, and also in other severe anæmias, and produce some resemblance to the histological features of leukæmia—an aspect of the subject which we have stressed in a later section (Part IX).

ERYTHROBLASTOSIS.—The erythroblastic changes found, especially in the liver in which there is the embryonic type of blood formation, may lead to confusion with myeloid metaplasia. When such histological changes accompany severe erythronoclastic anæmia of the new born, the similarity to leucosis becomes even closer. The clinical features are dealt with in another article of this series (Part IV), and the morphology of the cells in another section of this paper.

COOLEY'S ANÆMIA.—This form of erythroblastæmia[14, 15, 16] can be partly differentiated from leukæmia by its racial incidence, being confined to children of Mediterranean races; by the bony changes as revealed by radiography; and by blood examination, which shows an enormous number of normoblasts and some megaloblasts in the blood stream.

CONDITIONS WITH LEUKÆMOID BLOOD PICTURES.—A large number of conditions give blood pictures which may closely simulate those of leukæmia.

Septic granulocytosis.—In severe sepsis, extreme degrees of immaturity of the white cells may be rarely encountered, and even myeloblasts may be present (Krumbhaar[17], and Herz[18]), a condition which resembles one of our examples of myelosis in which myeloblasts were few.

Septic lymphocytosis.—Sepsis and infective conditions have also long been regarded as occasionally causing absolute lymphocytosis. Tidy[19] has reviewed most of the records of such cases and has concluded that the case for lymphocytosis in inflammatory conditions is not proven and that many, if not all, of the alleged cases were really examples of infective mononucleosis or glandular fever. However, it appears that not uncommonly an infective process may lead to a relative lymphocytosis on account of an overwhelming depression of the myeloid series (Talley Griffith[20]). Piney has pointed out that eosinophils and platelets are often not reduced, and considers that this indicates a defect in emigration rather than an aplasia.

Glandular fever.—Owing to the swelling of the lymph glands, this disease may closely simulate leucosis. In contrast, it shows little or no anæmia and no diminution of platelets. The characteristic mononucleosis consists usually of an absolute increase in lymphocytes and more rarely of monocytes. The all important point again is the mature nature of the mononuclear cells. In this condition remission may occur and the mononucleosis may persist after clinical recovery; thus the accidental finding of a lymphocytosis may be explained by a previous attack of the disease.

Post-infective and post-hæmorrhagic lymphocytosis.—On recovery from infective conditions which have produced a granulocytosis, a relative lymphocytosis, with return of eosinophils may occur, but because of the mature character of the cells and the presence of eosinophils, and a good number of platelets, this will only rarely simulate lymphatic leukæmia.

Hæmorrhages of long duration may also be a cause of relative lymphocytosis and increase in eosinophil cells, the red cells showing changes including polychromasia and microcytosis. It should be emphasized that the lymphocytosis here is relative; absolute lymphocytosis occurs in few conditions, examples of which have been given.

Other specific infections.—Leukæmoid blood pictures may be associated with specific infections such as measles, whooping cough, diphtheria, chicken-pox. The following example of such a condition in congenital syphilis illustrates the difficulty of diagnosis.

T. C., aged 3 months. Complaint was made of epistaxis two days before admission and of a rash on the legs and arms. Bleeding from the rectum had occurred three weeks before. On examination:—intense anæmia; a brownish, slightly raised rash on both legs and pemphigoid eruption on the left side of the scalp; spleen enlarged one inch; liver enlarged. The course in hospital was afebrile. Blood examination: R.B.C. 1,600,000; Hb. 18 per cent.; C.I. ·56; W.B.C. 20,100; platelets 20,000. Differential count: neutrophil p.m.n. 15 per cent.; eosinophil p.m.n. 3·5; basophil p.m.n. ·5; n. meta. 2·5; large lymphocytes 72·5; small lymphocytes 0; Türck cells 1·0; monocytes 5. Red cells pale, aniso- and poikilo-cytosis, slight poly-chromasia, one normoblast found, platelets few in the film. Wassermann reactions of child and both parents were strongly positive.

Though there were clinical features which suggested the true diagnosis, from the hæmatological standpoint the only clue was the definitely mature character of practically every one of the lymphatic cells present. As against all other features, the characters of the suspicious cells cannot be over-emphasized. A drawing of these cells is found in Fig. 18.

AGRANULOCYTIC ANGINA AND APLASTIC ANÆMIA.—In aplastic anæmia, there are anæmia, thrombopenia, usually leucopenia with relative lymphocytosis, and sometimes splenomegaly. The mature characters of the lymphocytes should distinguish this condition from aleucocythæmic lymphadenosis, but difficulty would occur in differentiation from aleukæmic lymphadenosis. The latter would tend to have a normal or slightly increased total of white cells, and probably a more acute course. Aplastic anæmia may be a phase of an erythronoclastic anæmia, and aplastic blood pictures of the erythron are often seen in the leucoses, especially in the later stages. According to the conception of Lescher and Hubble[21], only one of the three elements (erythron, white cell and blood platelet systems) of the hæmopoietic apparatus may be damaged and, in this way, aplastic anæmia, agranulocytic angina and thrombo-cytopenic purpura may arise. Bigler and Brennemann[22] have collected cases of agranulocytic angina in children, where the severe leucopenia of even 800 leucocytes, would distinguish the condition from aleucocythæmic lymphadenosis. In the event of severe hæmorrhage, causing anæmia, thrombo-cytopenic purpura might simulate aleucocythæmic leucosis.

BANTI'S DISEASE.—Splenic anæmia of the adult type, though rare, is occasionally met in children, and it has been seen as early as two-and-a-half years (Parsons). Hæmatemesis and leucopenia are usual, and together with the histological findings of fine cirrhosis distinguish the condition from leucosis.

OSTEOSCLEROSIS FRAGILIS GENERALISATA (ALBERS-SCHÖNBERG'S DISEASE).—This rare disease usually shows blood changes of leukæmic type and therefore may lead to diagnostic difficulties; the following is an instance which came under our observation:—

A girl of 8 months, who had always been pale, developed double proptosis and rotary movements of the eye. Examination revealed a large head with distended veins, marked anæmia, splenomegaly, slight glandular enlargement and optic atrophy with 'pepper and salt' fundi. The blood examination showed: R.B.C. 3,300,000; Hb. 65 per cent.; W.B.C. 50,000. Differential count: 19 per cent. myelocytes, 13 per cent. myeloblasts, 11 per cent. fractured immature cells; 7 normoblasts and 3 megaloblasts per 100 W.B.C. Radiograms of all the bones showed typical changes: normal contour, except for fractures, but all spongy bone and marrow transformed into compact bone. Death occurred at the age of 11 months. At autopsy the outstanding feature was the replacement of spongy bone by dense bone and the absence macroscopically of marrow; at the ends of the long bones osteoid tissue was found. Histologically the bones showed small islets of myeloid tissue, which often surrounded the blood vessels and were present also in the cartilage; myeloid metaplasia was present in the liver and lymph glands. The

immaturity of the granulocytes in the peripheral blood and the myeloid metaplasia suggest a relationship with myelosis. It is interesting to speculate whether the blood changes preceded and caused the bone changes, or vice versa.

RETICULO-ENDOTHELIOSES.—There is a group of somewhat widely differing diseases, of which the commonest is Hodgkin's disease, which may be grouped under this heading. Hodgkin's disease is accompanied by a more pronounced glandular enlargement than the leucoses and the blood picture is not leukæmic in character. The so-called storage reticulo-endothelioses—Gaucher's, Niemann-Pick's, and Christian's diseases—may, on account of anæmia and spleno- and hepato-megaly, clinically resemble leukæmia, but the blood picture is entirely different.

Of recent years several cases of reticulo-endotheliosis in children have been reported, mainly by German workers, and we have recently observed four cases, with somewhat similar features. A full description of these cases will be given in Part IX, and it is evident that many features: anæmia, enlargement of liver, spleen and/or lymph glands, may cause confusion with leucosis, but neither lymphatic nor myeloid leukæmic cells are found in the blood stream.

OTHER FORMS OF LEUKÆMIA.—There are certain other forms of leucosis which may be mentioned. Lymphosarcoma simulates lymphadenosis in many ways and the process seems to differ only in the lesions being more focal in distribution; the blood counts may be similar to those of acute lymphatic leukæmia. A case of leucosarcomatosis was described by Parkes Weber[22] in a boy aged 7. The blood picture showed 103,000 white cells, of which 94·5 per cent. were myeloblasts. Histological investigation showed myeloid interacinous infiltration in the liver, myeloid metaplasia, including the presence of megakaryocytes, in the hilus of the kidney. Chloroma occurs most frequently in childhood; there is usually a blood picture of myelosis, and, though immature cells may be absent from the peripheral blood, the condition may be regarded as essentially the same as the ordinary leucoses.

Eosinophilic leukæmia is very rare (Hay and Evans[23]) and, according to Bass[24], only three cases in children have been reported.

The present study of leukæmia does not lend support to the conception of a mixed type, though immature cells of both the chief series may be found in the same case. As explained elsewhere, the cause of this is probably irritation of marrow by the invasion of foreign cells. Our cases have been remarkably pure in their hæmatological and histological features. However, many, e.g., Türck, Hirschfeld, Herz, Baar and Downey, have believed in the occurrence, though no doubt rarely, of true mixed leukæmias, and Logefeil[25], in reporting a case which he claims as an example, has carefully reviewed the literature.

Morbid anatomy of acute leucosis.—As a rule, naked-eye examination reveals no diagnostic feature. Extreme pallor with sometimes a few petechiæ; an inconstant degree of enlargement of the liver, but often much fatty change; considerable, slight or even no increase in the size of the spleen

with little alteration in texture or appearance; congestion with little or no swelling of lymphoid tissue; an atrophied or normal-sized thymus; frequent ecchymoses and a thrush-breast appearance of the myocardium; terminal broncho-pneumonia and scattered small irregular hæmorrhages into the pleuræ; a light or dark red cellular marrow: such are among the usual findings in infants and children. Nor could myelosis be differentiated from lymphadenosis with certainty, though our two cases of the former type showed greater enlargement of the lymph glands and spleen than some of the lymphatic cases, and they both displayed a slightly grey tint in the red colouring of the marrow, which was not noted in the lymphatic cases.

A point of interest is that none of our cases has shown enlargement of the thymus gland, nor have histological abnormalities been present where this organ has been examined. This suggests that the small thymic cells are not lymphocytes and are of different origin.

Microscopic morphology.—The morphology of the leucotic cells as seen in films of the peripheral blood and in the tissues is of the utmost importance in the study of leucosis, both from a diagnostic and an ætiological point of view. In this study blood films have usually been made on cover slips, and Leishman's and Panoptic stains have been used. In the examination of tissues, to define the cytological features, the thinnest possible sections, not exceeding 4μ, and preferably 3μ, thick have been necessary and the use of a one-twelfth oil immersion lens almost essential. An ocular micrometer has proved a useful adjunct. Oxydase staining has sometimes been employed, but, before its use, the type of the leukæmia has usually been fairly clear from the examination of the blood films. Except in special circumstances, when obviously unusual forms are present, vital staining does not appear to assist very much; indeed, Hall[26], after an extensive review of recent papers, concluded that polychrome stains assisted more than vital staining in the differentiation of blood cells.

Blood films and sections.—A real difficulty in the study of the blood and its formative tissues is the difference in appearances of cells in the blood films and in sections of tissues, however fixed and stained. Again, films made from pieces of tissue provide a picture of cells different from that of films made from the peripheral blood. The characters of the cells of the peripheral blood have been described by numerous workers, and a large number of drawings have been published, but far less attention has been paid to appearances of blood cells in sections and to their correlation with those of blood film preparations; indeed, the majority of authors fail to provide illustrations of cells in sections, comparable with those of the peripheral blood film. No doubt a great cause of the different appearances between the tissues and blood films is due to changes in the cells following death, for frequently even films made from the heart's blood within a few minutes of death are surprisingly disappointing in their staining properties. The lack of clear staining of the neutrophil granules in sections is one of the great obstacles. A good many methods have been tried to overcome this and so far the best results have been obtained with fixation by Helly-

Maximow solution, and subsequent treatment with iodine, followed by hyposulphite of soda. Jenner's or Panoptic stains (Jenner followed by Giemsa) have given definitely better revelation of neutrophil granules than Giemsa alone, although the latter is often recommended for this purpose.

In these studies an attempt has been made to correlate these different cytological appearances. Drawings of the cells under discussion are given in Fig. 1.

LYMPHADENOSIS.—In this condition in children the condition is so acute that lymphoblasts are rarely absent from the blood-stream and thus the diagnosis is easier than in the chronic forms of adults, where frequently only mature lymphocytes may be found. The results of our observations have indicated the necessity of modification of some of the published descriptions.

The lymphoblasts in the peripheral blood have generally been smaller than 12–18μ (the measurements given by Piney[27]): the smaller ones have measured 7 to 9μ, and the larger 9 to 14μ, with an occasional case showing forms up to 18μ; the cytoplasm has almost invariably been small in bulk, often scarcely discernible. A feature has been the irregularity of the nuclear contour: indentation has been present in many of the cells, while blunt lobulation has frequently been seen. The texture of the basi-chromatin has usually been finer than distinct stippling, though slightly coarser than that of the myeloblasts in one of our two cases of myelosis: the texture might be described as of a matt appearance, with fairly fine stippling in the more mature forms; condensation of the chromatin has not been marked round the nucleoli or nuclear membrane, but it was more than in the myeloblasts. Nucleoli have frequently not been easy to find, although some cells have shown one or two and rarely even four or five; small vacuoles in the cytoplasm of the cells with a more bulky cytoplasm have often been present. Türck cells have commonly been found, but the larger plasma cells have not been frequent in lymphadenosis.

Tissues have been fixed by formalin, neutral formalin and Helly-Maximow methods in different cases. No definite differences in cytological appearances have been noted by these various methods, except that there was more shrinking in the formalin-fixed tissues, proportionately to the length of time of fixation, and the myeloid cells in the marrow sections showed granulation better with the last method. In sections from cases of lymphadenosis, lymphoblasts, like other cells, have uniformly appeared much smaller than those in the blood films, their diameters being half to two-thirds in diameter, and their total cell area about one-quarter to one-half of the lymphoblasts in the blood films. The diameter of the cells has been fairly constant, being between 5 and 8μ, whereas typical lymphocytes in the same cases measured 3 to 5μ. Again irregularity of nuclear contour has been present, and its extreme degree has occasionally given some difficulty in identification. On careful focussing it is seen that this irregularity is sometimes complex and not merely the jutting off of a lobe. The appearance may be similar to that of a cigarette paper fairly loosely crumpled: the

twisting margin of the nucleus being comparable with the irregular folds of the crumpled paper. It is possible that this appearance may be partly due to some shrinking during fixation, but in sections, fixed in Helly-Maximow's solution and showing no shrinking, irregularity of nuclear shape has sometimes been well marked. In most of the sections the lymphoblasts have shown this crumpled appearance more than myeloblasts. The cytoplasm has been small in amount and the nuclei have stained a fairly dark blue throughout, overlaid by irregular and indefinite dots and threads of chromatin. Compared with the myelocyte, the nuclear size has been smaller, the colour darker, the nuclear margin heavier but less delicate and so less prominent and more irregular, and the chromatin deposits less sharply defined; granules have, of course, been absent. The cell is less vesicular in appearance and less conspicuous in the tissues.

Myelosis.—In blood films, the two cases of myelosis did not show many myeloblasts, most of the young cells being slightly granular, i.e. promyelocytes. The myeloblasts and promyelocytes were larger than lymphoblasts and measured 11 to 18μ with nuclei of 7 to 15μ in diameter. The cytoplasm was more bulky than in lymphoblasts, but in some cells was small in amount; in some cells the cytoplasm was paler near and round the nucleus. On the whole there was less irregularity of nuclear outline, the texture was finer and somewhat sponge-like, and sometimes showed a faintly staining delicate network and streaking; nucleoli were more frequent than in lymphoblasts. Rarely mitoses were found in the peripheral blood. Monocytoid myeloblasts have been described fairly frequently in myelosis; and these, with other forms of monocytosis in myelogenous leukæmia have been referred to in Part VII. On the whole the above characteristics apply to a large number of cells, though individual cells are not always capable of identification as myeloblasts or lymphoblasts. It is, of course, rare for the blood picture of a myelosis to fail to show any signs of granulation in some of the cells, especially when oxydase staining is used.

In the tissues myeloblasts appear smaller than in blood films though larger than lymphoblasts as indicated in Fig. 1 (22, 23, 31 to 36). The cell usually appears round or oval with a definite amount of cytoplasm, surrounding a round or oval nucleus of which the margin is more regular and delicately cut than in the lymphoblast. This clearness of the nuclear margin is largely due to the paler staining of the interior, which shows less well marked dots, threads and irregular masses of chromatin than the lymphoblast; some cells show nucleoli and smaller deposits of karyomitome. These features are displayed better in the myelocyte and promyelocyte. In a normal marrow, if neutrophil granule staining is successful, it will be found that most of the cells with the above-mentioned characters are in fact promyelocytes, whereas a smaller number of cells, which have less well defined features and stain more palely, are myeloblasts. Probably the outstanding point in the differentiation of young myeloid

cells from lymphoblasts is that of their paler " vesicular " appearance and larger size. In the lymphoblast and lymphocyte, the oxy- and basi-chromatin are not so well defined one from the other, and combine to give a nucleus more deeply stained and with indefinite darker markings, whereas the nuclei of the myeloblast and myelocyte show a paler groundwork with one or two nucleoli and a few clearly defined condensations of chromatin in their interior. An attempt has been made to depict these characters to scale, in Fig. 1.

Possibly of equal help in cytological diagnosis is the determination of the direction of maturation: whether towards the lymphocytic or myeloid series of older cells. Only rarely do acute cases fail to show adolescent, if not older cells, indicating the family to which the young forms belong.

Differentiation of myelopoietic from erythropoietic foci.—In the tissues immature forms of hæmoglobin-containing cells, i.e., erythroblasts, are sometimes difficult to differentiate from myeloblasts and myelocytes; indeed, this may be impossible with the most immature forms of the pro-erythroblast. However, the differentiation of foci of erythropoiesis, such as are seen in the liver in premature infants, in icterus gravis, in hydrops fœtalis and in hæmolytic anæmia of the new born, is important both from a cytological point of view and in relation to the study of leukæmia. Pinkerton[28] states ' it must be admitted that there is no positive method of distinguishing in fixed tissues between the myeloblast and the early megaloblasts,' and with this we would agree. Ellermann and Petri give the angle of mitosis of myeloblasts as 60 and that of the erythrogonium as 20. Megaloblasts are scanty in normal bone marrow and frequently, though erythropoiesis is active, cannot be definitely identified. Working on smears of bone marrow, prepared according to Isaacs'[29] technique we have found only three or four megaloblasts after searching through preparations from a number of different cases. Even the finding of this small number, however, would appear to exclude their restriction solely to a type of embryonic hæmatopoiesis in the liver and spleen, as is claimed by some. In cases of erythroblastosis, however, cells are often found in the hepatic sinusoids which have characters suggesting that, in stained films of the peripheral blood, they would give the appearance of the typical megaloblast.

The term erythroblast appears a suitable term to connote any stem cell which appears to be a maturing hæmoglobiniferous cell, and in this paper this term is used for any immature cell which appears to be a precursor of an erythrocyte, i.e., it includes both megaloblasts and normoblasts. In sections of erythropoietic foci some cells are found which, allowing for the difference in appearances of sections and blood films, appear to correspond with the megaloblasts of the blood stream whereas some cells appear to be more immature. The latter probably correspond to erythrogonia of some writers and have been called by us ' pro-erythroblasts.' Sabin, however, uses the term erythroblast to designate only early and late types

of normoblast, and megaloblast for cells which are more immature than these. The terms used here may be arranged as follows—

Pro-erythroblast (Erythrogonium)
↓
Erythroblast { megaloblast; young normoblast; normoblast { macro-normoblast; micro-normoblast }
↓
Erythrocyte

Normoblasts, if large, are termed macro-normoblasts, and, if small, micro-normoblasts. It is not certain that the above arrangement necessarily represents the sequence of maturation, for it is possible that, for example, a megaloblast may develop into an erythrocyte without passing through a normoblastic stage.

In erythroblastosis of infants (see Part IV) it is usually seen that erythropoiesis in the liver preponderates over, and even excludes, leucopoiesis. Apart from a few myeloid cells, the cells found in extra-medullary embryonic erythropoietic foci may be described as follows.

The most immature cells, which are usually not numerous, are fairly large pale cells with lightly staining nuclei and a rather lightly staining cytoplasm. We have called these pro-erythroblasts or erythrogonia. The next cells in the series are more numerous and prominent; they are fairly large oval or round cells, 8–10μ in diameter with a moderate amount of cytoplasm, which frequently stains more deeply with hæmatoxylin or methylene blue than does that of myeloblasts. The nuclei are about 7μ in diameter, vesicular and similar to myelocytic nuclei, though there is a tendency for the knots of karyomitome to be fewer, larger and more distinct and to lie nearer to the nuclear membrane. On the whole, as compared with promyelocytes and myelocytes, the cytoplasm and nuclear chromatin stain more darkly, or stand out in greater contrast against a rather paler karyoplasm. It is not certain whether these cells emigrate into the blood stream; if so, they would no doubt appear as that kind of megaloblast with a fairly streaked nucleus and basophilic cytoplasm; if not, we may include them with the pro-erythroblast.

The cell which appears to correspond most closely with the megaloblast of the blood stream is slightly smaller (about 7μ) and definitely darker in the staining of all its components: the cytoplasm is darker blue, the nuclear membrane heavier and the karyoplasm darker. But the striking difference is the heavy dark stippling, distributed evenly throughout the nuclear area, similar to the appearance in blood films.

The young normoblasts are often more numerous than any of the foregoing and their characters form a transition to the normoblasts. These young normoblasts are smaller than megaloblasts, dark, and show in their round nuclei a few indistinct heavy masses of chromatin, sometimes arranged in cart-wheel fashion; their cytoplasm is small in amount and

more eosinophilic than the foregoing cells. The remaining normoblasts are older and display a small round blue-black nucleus, devoid of markings, in a thin or thick rim of eosinophilic cytoplasm. Some of these may show marked degrees of pyknosis, even simulating polymorph granulocytes in their shape, but can be differentiated from them by the deep-staining properties of the nuclei and their smaller size. Scattered whole nuclei and nuclear fragments are also usually to be found. In some sections it has at times been difficult to differentiate young normoblasts from normal lymphocytes on individual cytological features alone. As described above, the young normoblasts show some dark chromatinic markings as does the lymphocyte: nevertheless, by comparing specimens of the two, from regions where there was little doubt as to their identity, it has usually been found that the young normoblast is slightly smaller (about 4μ as against 5μ), its cytoplasm more eosinophilic (yet small in amount), its nucleus darker and the chromatin deposits fewer and more deeply stained than is the case with the lymphocytes. In somewhat over-stained sections these differences will be more or less obliterated.

The cytological features of embryonic erythropoiesis have been dealt with in some detail because of the importance of differentiating them from myeloid metaplasia in myelosis. Sometimes the proportion of pro-erythroblasts is so high that differentiation from myelosis on the examination of one section may be impossible; indeed, it is probable that not a few cases of leukæmia reported in young infants have in fact been cases of anæmia showing erythroblastosis in response to a hæmolytic process.

The reticulo-endothelial system in leukæmia.—Practically all our cases have shown activity on the part of the reticulo-endothelial system, in the form of swelling and loosening of Küpffer cells; proliferation in the splenic reticulum, sometimes with the production of many reticulum fibres and at other times with the multiplication of cells with blunter processes; proliferation and freeing of the endothelium of venous sinuses of the spleen, and of the sinuses of lymph glands. Without going into the question of the origin of the histiocyte, which has been dealt with elsewhere[30], it appears probable that they arise from the reticulo-endothelium. Our cases have shown an increased number of histiocytes, particularly in the hepatic sinusoids. Typically these cells have a bulky and faintly eosinophilic cytoplasm as stained by hæmatoxylin and eosin; their shape is polygonal, caudate or irregular and their measurements vary greatly from 12 to 30μ in fixed sections. Their nuclei are usually faintly stained, often indented or bean-shaped and not uncommonly lobulated or bulbous; the interior possesses few markings, mainly some faint streaks and a few dots, but the latter are less numerous and distinct than in fibroblasts, which often show dotted or dusted nuclei. The nuclei are similar to those of swollen Küpffer cells, which are frequently seen and, if they are still partially attached to the walls of the sinusoids, may be identified with certainty. In fact, the study of our cases supports the conception that histiocytes arise

in part from endothelium in the liver, reticulum cells of the spleen and lymph glands, and probably from so-called germ centre cells of lymph glands. Some swollen cells will be found, however, with similar cytoplasmic and nuclear characteristics which suggest that they too are histiocytes. These cells may be as small as the average polymorphonuclear granulocyte —in the region of 6 or 7μ in sections—and owing to the fact that the nuclei are sometimes lobulated (in contra-distinction to segmented), they may closely simulate the granulocyte. The latter has typically, however, a darker nucleus with a heavier nuclear margin and well defined oxy- and basi-chromatin. The larger histiocytes will sometimes be seen to have ingested other cells and fragments, but phagocytosis has varied much in our different cases. Cells entirely similar to these histiocytes have been observed in large numbers in cases of anæmia with reticulo-endothelial reaction (Part IX).

Histopathology of leukæmia.—Passing on from purely cytological features, the architecture of the various leukæmic tissues is easier to describe and its features in the two chief forms easier to recognize.

Lymphadenosis. Liver.—The differences between the two types of leucosis are well shown. All the cases of lymphadenosis show definite infiltration of the portal tracts; these lymphomata may be small or large and they may also be accompanied by extensive permeation of the sinusoids. The combination with sinusoidal infiltration is shown well in Fig. 6. The sinusoids are swollen and loosened endothelial cells, with some histiocytes, often phagocytic, may be prominent. Fatty degeneration, especially of the central areas, is a feature.

Spleen.—This organ may show surprisingly little infiltration, though sometimes this is marked in both the capsule and pulp. The chief changes are fibrosis, hyaline change in arterioles, and a definite increase in reticulum cells. The nuclei of the latter are often paler and larger, and their cytoplasm has shown blunter processes than normal; the endothelial cells lining the sinuses show less proliferation than in myelosis. Some phagocytosis may be seen. The lymphatic cells of the follicles and in the meshes of the pulp are increased in number and often show the characters of lymphoblasts described above. The increase in size of the spleen is partly due to infiltration, but also to fibrosis and reticular proliferation, which appear to be reactive in nature. Preparations in which the reticulum is stained by Bielchowsky's silver method show an increase of reticulum fibres in some cases, but not in all.

Lymph glands.—The outstanding feature is packing of the whole tissue with lymphatic cells, so that it is difficult to pick out germ centres and sinuses. Some cases show some swelling of reticulum cell nuclei. One, which

was of longer duration than the majority of the cases, displayed considerable proliferation of endothelial cells of the sinuses and phagocytic histiocytes were numerous. A few eosinophil cells have been seen in some cases. Mitoses are found more easily in glands, but are somewhat less frequent than might be expected. The germ centres do not show evidence of any great activity. The lymphoblasts appear to reproduce themselves and not to arise de novo from the endothelium either of the germ centres or the reticulum.

Bone marrow.—This is usually diffusely infiltrated by lymphatic cells, most marked round the blood vessels. Reticulum and myeloid cells may be difficult to find. However, in the less acute cases, and in some acute ones, sections of marrow may show no infiltration; presumably the degree of infiltration may vary considerably in different parts of the marrow.

Kidneys.—Interstitial infiltrations, usually small and scattered, are frequently found, but the sections of some of our cases have failed to show them.

Lungs.—Areas of terminal broncho-pneumonia, collapse and compensatory emphysema are common. One or two cases showed consolidation with the alveoli filled with mucinous material, some red cells and large pigment-carrying cells. The sections of those cases examined did not show leukæmic infiltrations.

Other tissues.—No characteristic changes were found, apart from the infiltration of the brain substance in one case. Usually where small accumulations of leukæmic cells are encountered, it is seen that they are grouped around blood-vessels or lymph sinuses.

Preparations by the Turnbull-Huecke process for the demonstration of hæmosiderin, have shown much variation in the amount and distribution of the iron: generally it has been most marked in the liver cells on the periphery of the lobules, but in the spleen it has been scattered in an irregular manner and not obviously included in any particular cells.

Myelosis. Liver.—Fatty degeneration of the central areas of the lobules is more or less severe, even proceeding to small focal necroses. The sinusoids are widened, and throughout are scattered cells of various types. Two cases in the present series, and one recorded in Part VII, have not shown such prominent groups of cells as cases of erythroblastosis, nor so much myeloid metaplasia as in adults. The cells scattered throughout the widened sinusoids are myeloblasts; more mature cells of the granular series; erythroblasts; loosened endothelial (Küpffer) cells and histiocytes which are often observed to be in phagocytosis. It is thus evident that prominent areas of metaplasia are not an essential feature in the liver. The picture is somewhat similar to that of the cases of reticulo-endotheliosis which will

be reported in Part IX, except that more myeloid cells have been found, and proliferation of Küpffer cells and the number of histiocytes have been less.

Spleen.—The prominent features are a diminution of lymph follicles which contrasts with the increase in lymphadenosis, and proliferation of the reticulum cells and fibres, in the meshes of which are numbers of scattered myeloblasts, myelocytes, metamyelocytes and erythroblasts. Eosinophil cells may be plentiful. The nuclei of many reticular and sinus cells are swollen and some of the cells are wholly or partially free. On the whole the cases showed a more cellular type of proliferation on the part of the reticulum than the more reticular one in the lymphatic cases. One case showed marked proliferation and liberation of cells lining and venous sinuses.

Lymph glands—The general picture is similar to that of the spleen, though lymphocytes are more numerous throughout the tissue.

Marrow.—It is here that histological diagnosis may be most difficult, for although, especially in acute cases, it may be easy to discern the immaturity, yet it may not be easy to differentiate a less anaplastic myelosis from the response of a marrow to an acute infection. In both these conditions the degree of immaturity displayed may be very similar. Probably the most trustworthy indication is given by the state of erythropoiesis, which is not so suppressed in the great majority of acute infections as in a subacute myelosis. In adults, where the shafts of the long bones consist so largely of fat, the wide extension of myeloid tissue is in favour of myelosis rather than a reaction to infection, but in young children this criterion cannot be applied. At the same time, it is true that in myelosis there is always definite increase in cellularity, packing together of the cells and a striking failure to develop mature granulocytes: changes which although present in severe reaction to infection are not so well marked. However, in the case of a less anaplastic myelosis it may be impossible absolutely to exclude the possibility of a purely infective reaction. The importance of this fact is obvious in biopsies of the marrow for diagnostic purposes. In myelosis degrees of anaplasia of the myeloid tissue are found. In the most acute cases all the cells appear to be myeloblasts or the slightly larger pro-myelocytes, and erythropoiesis is at a minimum. In less acute cases fewer of these cells, but more myelocytes are found, while polymorphonuclear granulocytes are few. Reticulum cells are often seen. Eosinophil cells are frequently plentiful in less acute cases.

Other organs.—Such organs as the adrenal and pituitary glands may show areas of myeloid metaplasia, but this was not found in our cases. Turnbull-Huecke preparations did not show any characteristic distribution of the iron, which was, however, increased in quantity.

Treatment.—There is unfortunately little to record with regard to the treatment of leucosis in children. The disease is so uniformly acute that measures which have delayed the progress of chronic leukæmia in adults,

such as treatment with benzol, arsenic, application of X-rays, etc., have usually no time to be effective.

Various attempts to treat the condition are recorded in the literature. Vedel, Vidal and Laux[31] used radiotherapy with liver treatment, their idea being to stay the inhibitive action of the X-rays on erythropoiesis by the administration of liver. A suggestive paper on the use of arsenic was published by Forkener and Scott[32], who recalled the observations of Cutler and Bradford[33] in 1878 on the effect of potassium arsenite in reducing the blood cells in two normal cases, two cases of anæmia and one of leukæmia. Forkener and Scott obtained good results by using Fowler's solution 30 to 50 minims daily, but all their cases were of chronic myelosis. The idea of administering liver along with treatment by arsenic was adopted in the last case of acute lymphadenosis which we have had under treatment, but without any apparent effect on the rapid development of the disease.

Conclusions.

This study of cases of both types of leucosis in children has shown that: (1) macroscopic focal leukæmic deposits in the viscera in children rarely occur, the infiltration being of a diffuse nature; (2) the cytological characteristics are different but relatively constant in the two types, and the architecture is distinctive in various regions.

The histology of the third rare type of leukæmia—monocytic or histiocytic—has been dealt with elsewhere[30].

Although certain features of myelosis can be imitated by severe myeloid reaction in inflammatory disease, the profound anaplasia of myelosis, often obliterating all erythropoietic function, is an outstanding feature. Lymphadenosis is not imitated by any known process of infectious disease in man. The impression left, after cytological and histological study, is uniformly that leucosis is a neoplastic process. Leucocytosis and leucosis appear to be respectively hyperplastic and neoplastic phenomena and analogous to reparative processes and malignant focal new growths.

Baar and Stransky[1] favour Sternberg's view that acute leukæmia is infectious in origin and different in nature from chronic leukæmia. They point out that leukæmic changes, i.e., in the pharynx, provide a more ready means of entrance to pathogenic bacteria and that the immature leukæmic cells show less phagocytic activity than normal polymorphonuclear cells. Hence great caution must be exercised in assessing the part, which any infection accompanying leukæmia, plays in its causation. Here and there infectious processes occur in the course of some cases of leukæmia, yet isolated instances are not convincing evidence that the infections are not incidental but causal.

Summary.

1. A study of 14 cases of leukæmia in children is presented, which includes brief reference to two cases previously published elsewhere. Only cases in which autopsy has been obtained have been included.

2. All the cases were relatively acute; there were 11 cases of the lymphatic, two of the myeloid and one of the monocytic type.

3. The clinical, hæmatological and histological features have been detailed and special attention paid to cytological appearances in blood films and tissues. Support is given to the view that types of leukæmia are distinct and can be distinguished by various criteria.

4. The differential diagnosis of a variety of somewhat similar diseases, with special reference to erythroblastosis of infants, has been dealt with.

5. The bearing of a few outstanding features of the study on the question of the ætiology is briefly discussed.

It is a pleasure to express my appreciation of the help of my technical assistant, Mr. J. T. Hall, who has especially assisted me by the skilful preparation of a large number of thin histological sections, involving much painstaking work.

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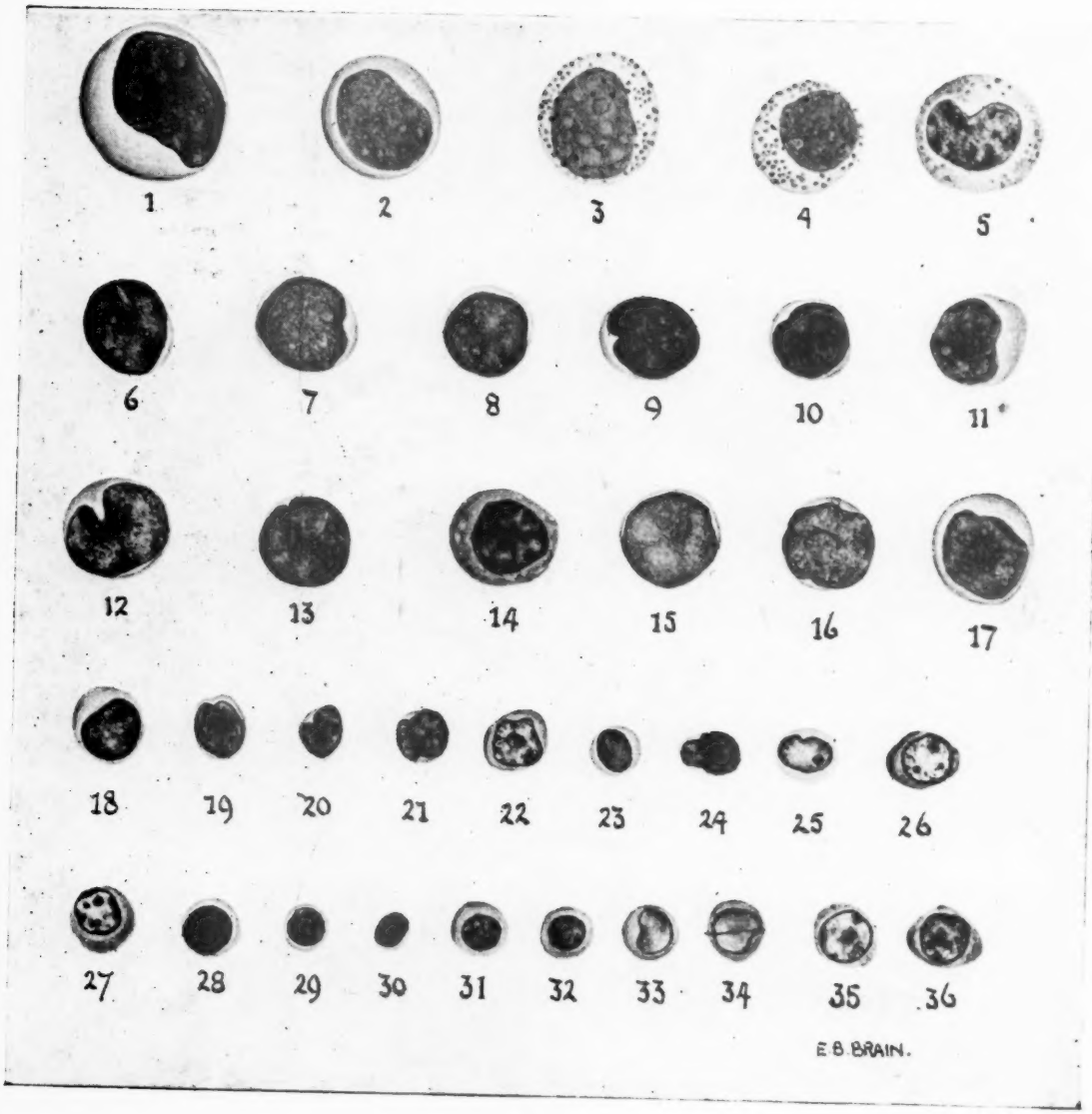
[For illustrations see pp. 314-322.]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E.B.BRAIN.

FIG. 1.

FIG. 1.—No. 1 TO 18 INCLUSIVE. Drawings of cells found in blood films of cases referred to. Magnification approximately 1,000 in all.
(Naegeli = *Blutkrankheiten und Blutdiagnostik*, O. Naegeli, Berlin, 1923.)

1. Myeloblast. Case T. W. Acute myelosis. Leishman (c.f. Naegeli, Tafel, X.1, XI).
2. ,, ,, ,, ,, ,, ,,
3. Promyelocyte. ,, ,, ,, ,, ,, (c.f. Naegeli, Tafel, X.2, XI).
4. Myelocyte. ,, ,, ,, ,, ,,
5. Myelocyte or young immature metamyelocyte in D. W., Leishman.
6. Lymphoblast. Case E. B. Acute lymphadenosis. Leishman.
7. ,, ,, ,, ,, ,, ,,
8. ,, ,, T. H. Acute aleucocythæmic lymphadenosis. Leishman.
9. ,, ,, ,, ,, ,, ,, ,,
10. ,, ,, G. M. ,, ,, ,,
11. ,, ,, K. W. Subacute aleukæmic ,,
12. ,, ,, L. P. Subacute lymphadenosis. Leishman.
13. ,, ,, ,, ,, ,, ,,

N.B.—The constantly small size of the lymphoblasts as compared with the myeloblasts and their greater tendency to irregularity of nuclear contour. Such lobed cells are often termed Rieder cells—see Naegeli, Tafel IX, 7. The nuclear texture, though fine, is slightly coarser, the nuclear staining somewhat deeper, the nuclear margin more heavily defined, and the cytoplasm less bulky than in myeloblasts. These characters do not necessarily apply to each and every cell, but obtain over a number. In myeloid leukæmia, a few, if not more, promyelocytes (No. 3, but perhaps with only a very few granules) will be found, especially if over staining or oxydase staining is employed.

14. Plasma cell in case E. B., Leishman.
15. Lymphoblasts.
16. ,,
17. ,, in K. W.
18. Lymphocyte, showing some immaturity of nuclear structure.

NO. 19 TO 20 INCLUSIVE. Drawings of cells found in tissues of leukæmic cases. Magnification in all about 1,000.

19. Case T. H. Acute lymphadenosis. Lymphoblast in section of liver, stained H.E., fixed in neutral formalin 24 hours after death in December.
20. Case E. B. Acute lymphadenosis. Lymphoblast in section of liver, stained H.E., fixed in neutral formalin 17 hours after death in November.
21. Ditto
22. Case D.W. Acute myelosis. Myeloblast in section of liver, stained H.E., fixed in formalin 12 hours after death in July.
23. Case T. W. Acute myelosis. Myeloblast in section of marrow, stained H.E.
24. Case K. W. Subacute aleukæmic lymphadenosis. Lymphoblast in section of liver, fixed in formalin 10 hours after death in February.
25. Case T. W. Acute myelosis. Myeloblast in section of lymph gland.
26. Case Cus. Icterus gravis. Pro-erythroblast in section of liver, fixed in neutral formalin 33 hours after death in October. Stain H.E.
27. Case Wa. Severe anæmia of newborn. Pro-erythroblast in section of liver, fixed in formalin 4 hours after death in January.
28. Case Car. Icterus gravis. Megaloblast in liver, fixed in formalin 14 hours after death in December.
29. ,, ,, Normoblast ,, ,, ,,
30. ,, ,, Normoblast ,, ,, ,,

(Cells 28 appeared to constitute transition forms between 27 (pro-erythroblast) and 30 (normoblast), c.f. tafel XVI, Naegeli.)

31. Case T. W. Acute myelosis. Myeloblasts from liver, stained H.E., fixed in formalin.
32. Ditto ,, ,, ,, ,,
33. Ditto ,, ,, from marrow ,,
34. Ditto ,, ,, ,, ,,
35. Case D. W. Acute myelosis. Myeloblast from marrow, stained H.E., fixed in formalin 12 hours after death in February.
36. Case D. W. Acute myelosis. Myeloblast from marrow, stained H.E.

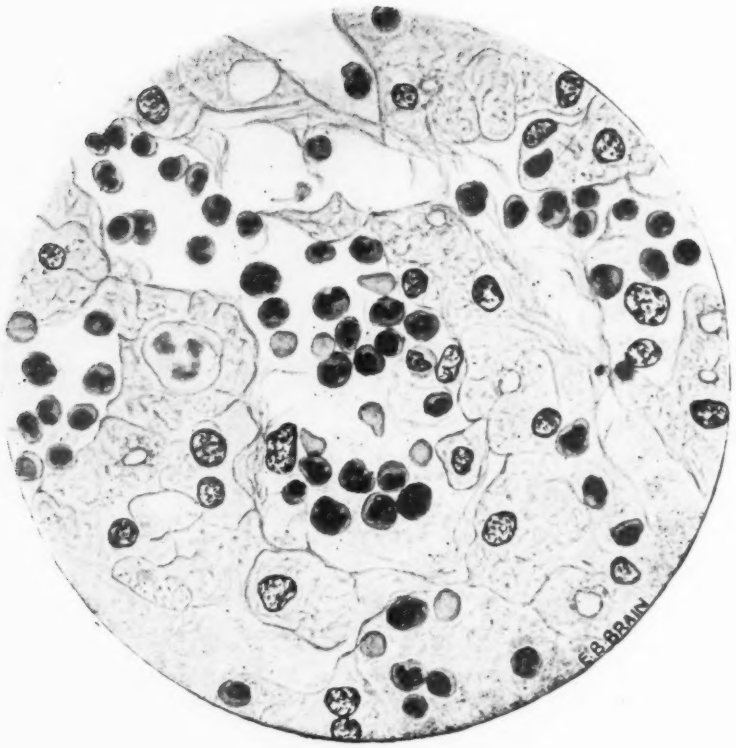

FIG. 2.—Projection drawing of liver in case K. W., acute aleucocythæmic lymphadenosis, showing a liver sinusoid, packed with dark cells with unusually irregular nuclei, the edges of which were rather indistinct (see Fig. 1 (11 and 17) and Fig. 7). The swelling of the endothelial (Küpffer) cells is well shown. × 1000. Fixed in formalin 10 hours after death in February.

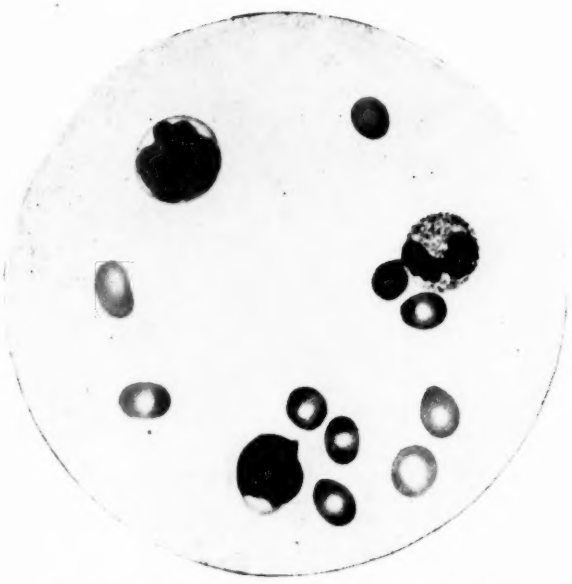

FIG. 3.—L. P. Subacute lymphadenosis. Blood film × 700. Leishman. Two lymphoblasts, top left cell showing 2 clear nucleoli, and bottom cell one. Note tendency to irregularity of nuclear contour.

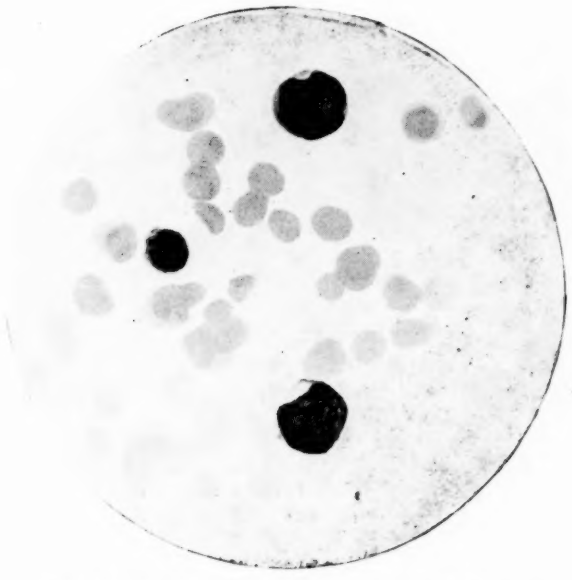

FIG. 4.—G. M. Acute aleucocythæmic lymphadenosis. Blood film × 700. Leishman. Two lymphoblasts and a darkly staining small lymphocyte. The top lymphoblast shows a tendency to somewhat larger masses of basi- and oxy-chromatin in the nucleus than do myeloblasts (see Fig. 12 and 13). Nuclear irregularity again apparent.

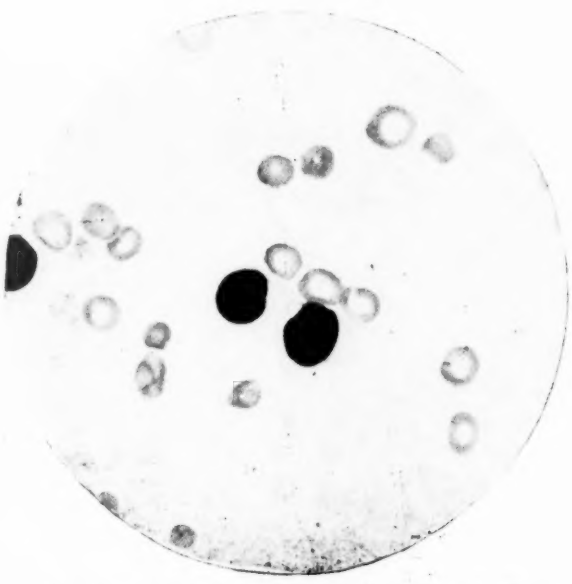

FIG. 5.—Acute lymphadenosis. Blood film × 700. Leishman stain. This case was remarkable in showing a mature type of cell: the cells shown do not apparently differ from lymphocytes.

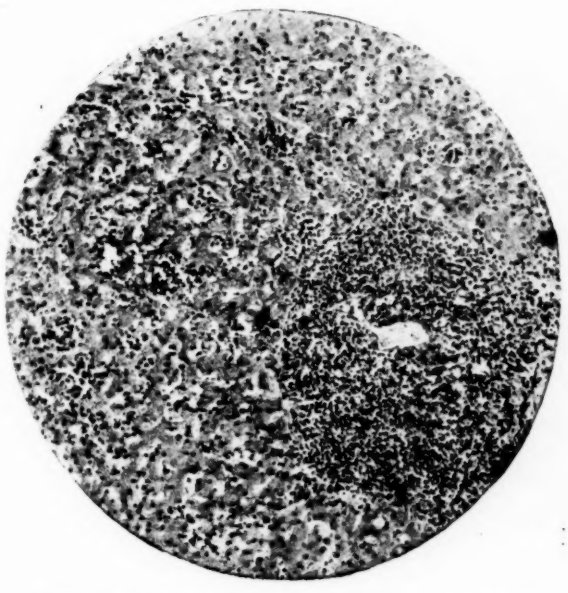

FIG. 6.—K. W. Acute lymphadenosis. Liver × 90. Stain H.E. Fixed in formalin 10 hours after death in February. Both extensive periportal and intrasinusoidal infiltration.

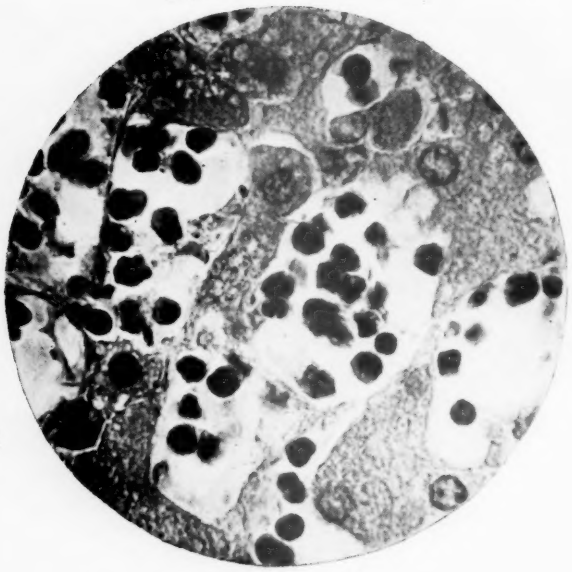

FIG. 7.—K. W. Acute aleukæmic lymphadenosis. Liver × 700. Stain H.E. Fixed in formalin 10 hours p.m. in February. Liver sinusoids packed with dark cells with remarkably irregular nuclei, of which the edges are not sharply defined. Compare Fig. 2, 1 (24). The nuclear irregularity was a striking feature of the lymphoblasts in the tissues in this case, but the other cellular features and the distribution of the infiltrations in the tissues revealed the type of the process.

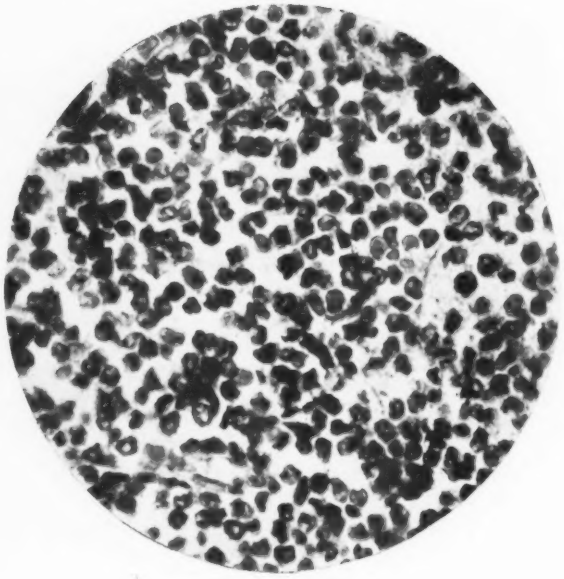

FIG. 8.—L. P. Acute lymphadenosis. Lymph gland × 525. Stain H.E. Fixed in formalin 30 hours p.m. in December. The irregular contours of the immature lymphoblasts are well shown.

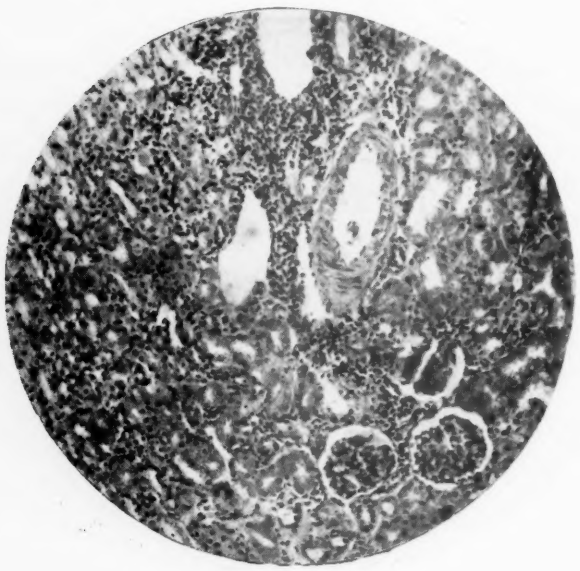

FIG. 9.—S. M. Acute lymphadenosis. Kidney × 90. Fixed in formalin 27 hours p.m. in April. Typical interstitial infiltration.

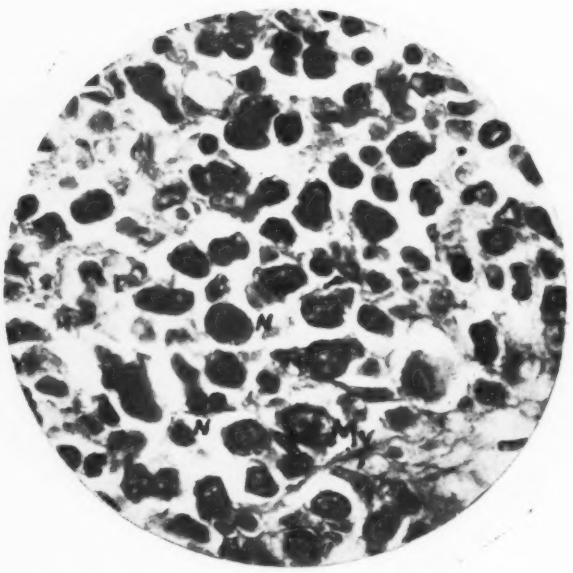

FIG. 10.—S. M. Acute lymphadenosis. Kidney pelvis × 700. Fixed in formalin 27 hours p.m. in April. While searching section 9, this small group of cells of a character entirely different from those infiltrations elsewhere in the tissues in this case, was found. The photograph shows the myeloid character: cells MY, appeared to be myeloblasts or promyelocytes, while normoblasts and macronormoblasts, N. are scattered throughout the focus. The myeloid focus is probably an extramedullary embryonic hæmatopoietic 'rest,' (as described by Shaw Dunn and others) called into activity by the severe anæmia accompanying the lymphadenosis.

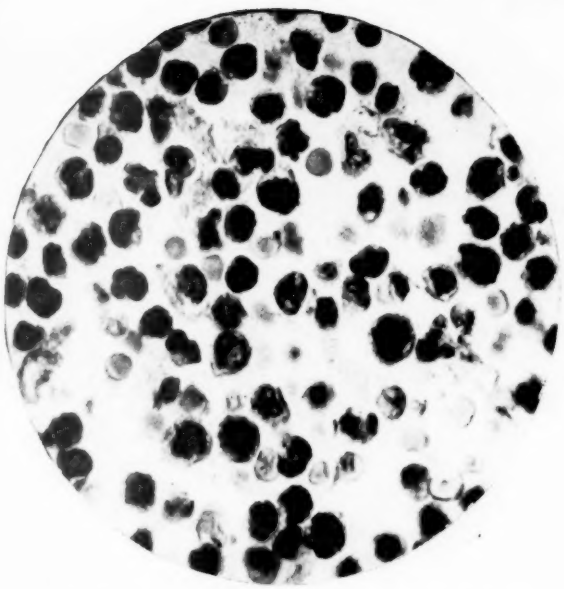

FIG. 11.—K. W. Subacute aleukæmic lymphadenosis. Marrow × 725. Stain H.E. Fixed in formalin 10 hours p.m. in February. The irregular contours of the nuclei of the lymphatic cells in this case are well shown. Practically no myeloid cells were found in this section. Macroscopically the marrow did not show any leucotic deposits.

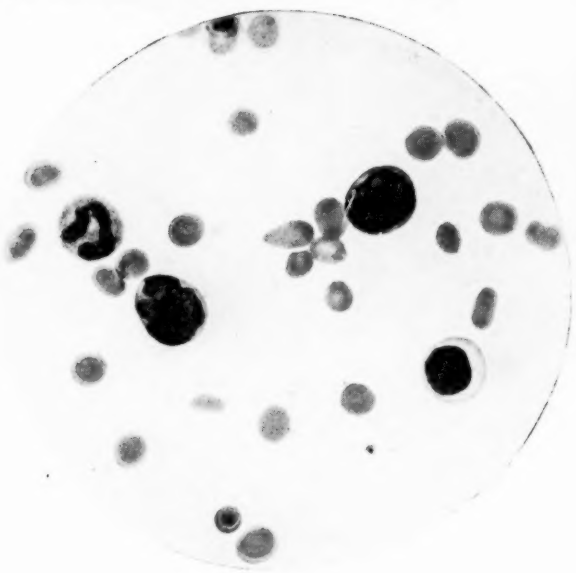

FIG. 12.—Acute myelosis. Blood film × 700. Stain Leishman. Two myeloblasts are shown in which the nucleoli appear faintly. The nuclear network and membrane are slightly more delicate than in the cases of lymphadenosis.

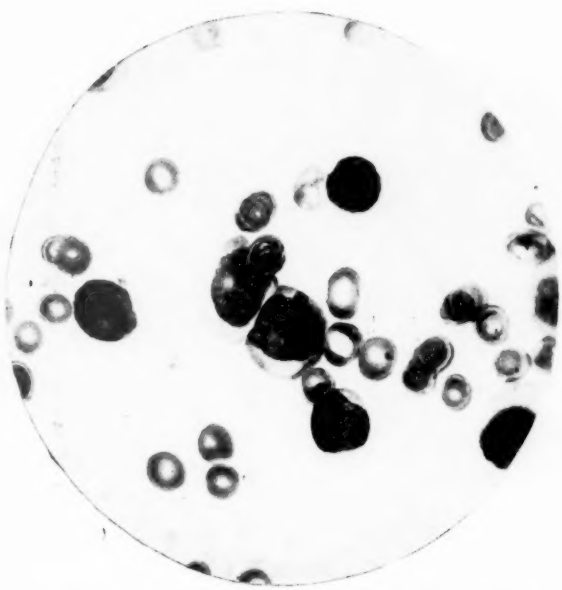

FIG. 13.—T. W. Acute myelosis. Blood film × 700. Panoptic stain. Note tendency for threading in the nuclei. Some of the cells showed slight granulation in the cytoplasm—promyelocytes.

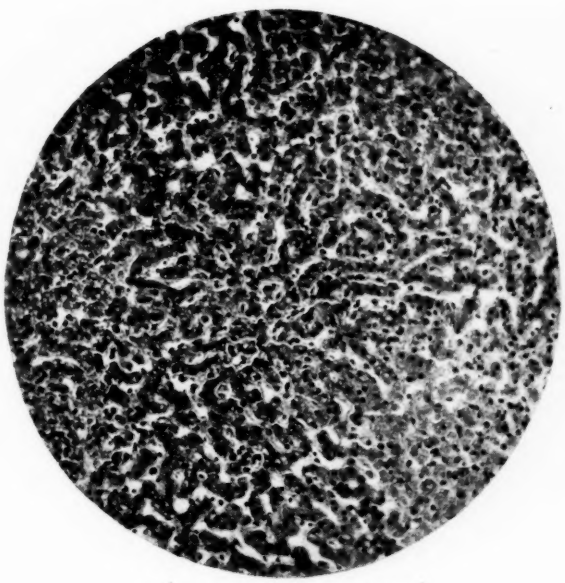

FIG. 14.—D. W. Acute myelosis. Liver × 90. Stain H.E. Fixed in formalin 12 hours p.m. in July. Liver sinusoids wide and containing infiltrating cells, some appearing large —myeloblasts. No periportal infiltration.

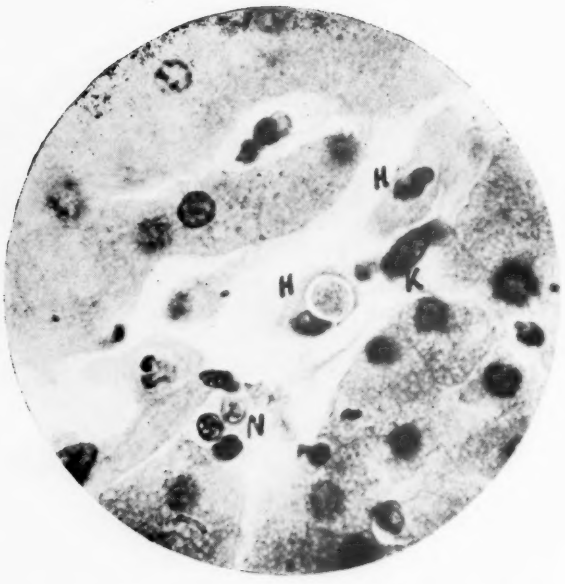

FIG. 15.—T. W. Acute myelosis. Liver × 700. Stain H.E. Fixed in formalin. Two histiocytes, H, one containing an ingested nucleus in a vacuole, and one swollen Küpffer cell K, shown. The cells N show appearances, suggesting they are immature normoblasts.

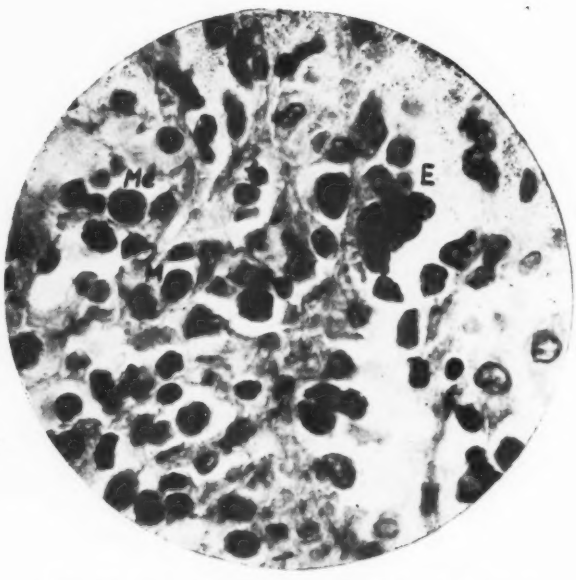

FIG. 16.—T. W. Acute myelosis. Spleen × 700. Stain H.E. Fixed in formalin. The endothelium of the venous sinuses was throughout much swollen and proliferated, as shown at E. Most cells in the reticulum appeared to be lymphocytes, but M may be a young myeloblast and Me a metamyelocyte.

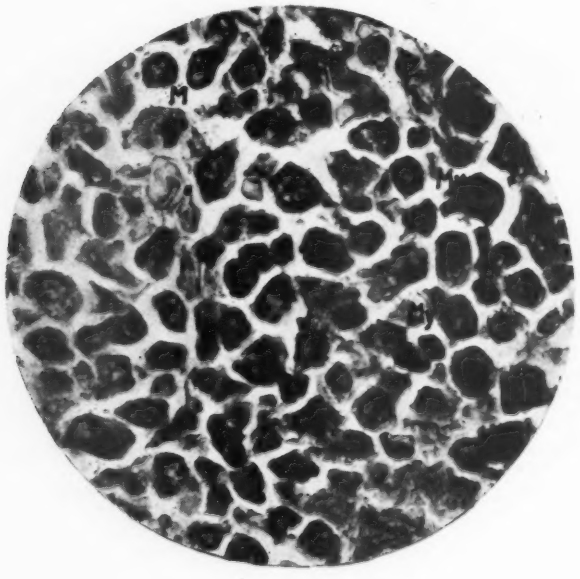

FIG. 17.—D. W. Acute myelosis. Marrow × 700. Stain H.E. Fixed in formalin 12 hours p.m. in July, after decalcification. Cells consist of myeloblasts, M, and myelocytes, My, the latter sometimes showing indefinite granulations; scarcely any erythroblasts, a few scattered erythrocytes.

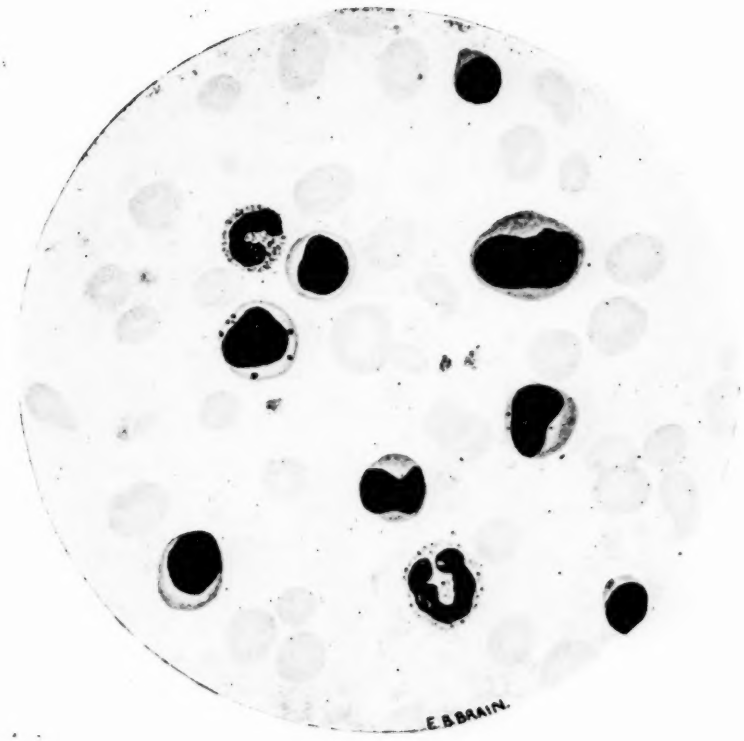

FIG. 18.—Composite drawing of blood film of Case T. O. Leukæmoid reaction in congenital syphilis. The entirely mature characters of the lymphocytes is noteworthy and contrasts with their appearance in lymphatic leukæmia.

Red cells, 1,600,000; Hb., 18 per cent.; white cells, 20,000; lymphocytes, 72·75 per cent.; platelets, 20,000.

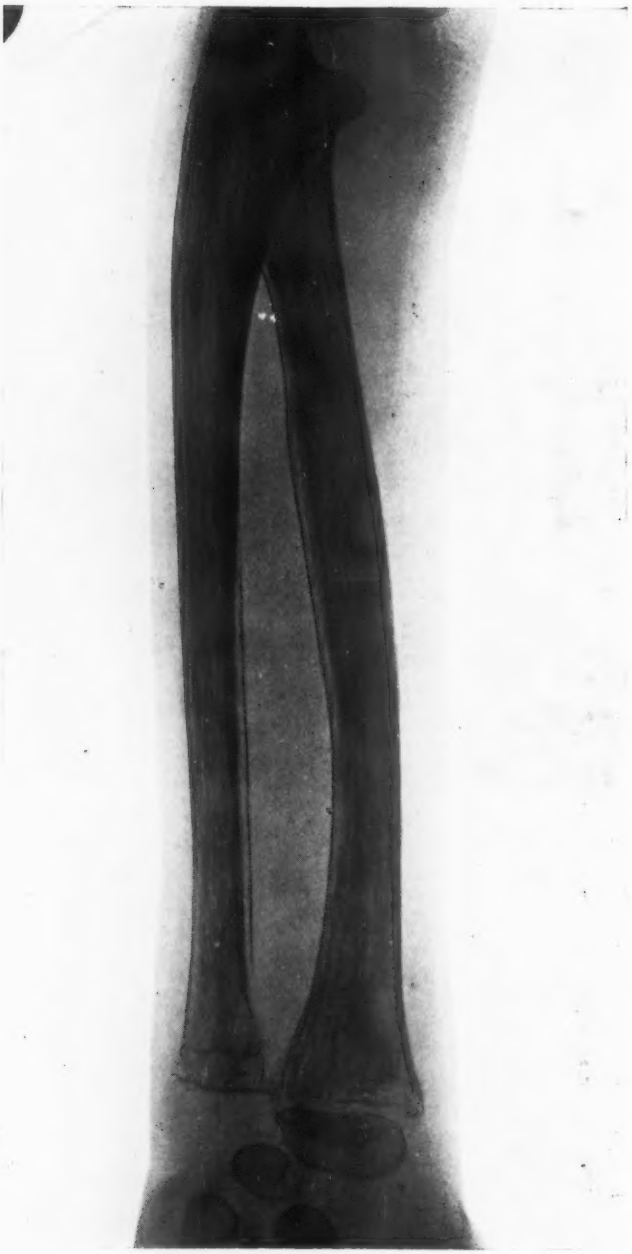

FIG. 19.—Lymphadenosis (J. B.). Cortical thinning and periosteal elevation with layering.

ON THE INCIDENCE OF CONGENITAL HYPERTROPHIC PYLORIC STENOSIS IN THE 17th AND 18th CENTURIES

BY

C. E. KELLETT, M.D., M.R.C.P.,

(From the University of Durham College of Medicine, and the Babies' Hospital, Newcastle-on-Tyne.)

The clinical picture presented by hypertrophic pyloric stenosis in the child is so distinctive that it seems improbable that such a condition, had it been as common as it is now, should have failed to attract attention before Hirschsprung's[1] presentation of two cases in 1888. There has been, therefore, on the one hand, a tendency, initiated by Osler[2] in 1903 with his reprint of the case reported by Beardsley[3] in 1788, to search the literature for earlier descriptions of the condition; and on the other hand room, possibly, for speculation whether any change in the modern mode of life could have favoured the development of this condition, the ætiology of which is unknown.

During the past six years three isolated and earlier examples of this condition have been recovered; Foote[4] has called attention to the case described by Armstrong[5] in 1771, Still[6] to that by Weber[7] in 1758, and Caulfield[8] to that described by Blair[9] in 1717.

Recorded by Patrick Blair[9] (1717). A male infant who at ' a month old was seized with a violent vomiting and a stoppage of urine and stool. Some time after both these became more regular, but the vomiting still continued.' He died at 5 months, very emaciated and weighing no more than 5 lb. Post mortem ' the ventriculus was more like to an intestine than a stomach, its length being 5 inches and its breadth but one inch . . . The pylorus and almost half the duodenum were cartilaginous and something inclined to an ossification.'

Recorded by Christopher Weber[7] (1758). Female, newly born infant. ' Sucked milk without difficulty but soon after she had filled her stomach with this infant nourishment she returned it by vomiting.' She died on the 6th day. Post mortem ' the pylorus was hard to touch like cartilage, and contracted. On incision its substance was seen to be thick, and the tightness of its contraction made the lumen similar.'

Recorded by George Armstrong[5] (1771). An infant, sex not stated, suffered from ' watery gripes,' and died at about 3 weeks old. Post mortem ' I found most of the stomach . . . in the same tender state, but towards the pylorus the structure was firm enough as likewise that of the intestine . . . the stomach was quite distended with curdled milk and victuals . . . but the whole intestines were remarkably empty . . . it looked as if the disease had been chiefly owing to a spasm in the pylorus.'

Recorded by Hezekiah Beardsley[3] (1788). A male infant showed from the first week ' puking . . . of the milk and of every other substance almost instantaneously . . . The feces were small in quantity . . . yet seemed otherwise pretty well . . . yet more lean.' He died at the age of about 5 years. The account of the necropsy contains the following:—' The esophagus was found greatly distended . . . from one end to the other of this tube, between the circular fibres which compose the middle

coat were small vesicles, some of which contained a table-spoonful of a thin fluid like water, and seemed capable of holding much more. I next examined the stomach, which was unusually large . . . it contained about a wine pint of fluid exactly resembling that found in the vesicles . . . The pylorus was invested with a hard compact substance, or schirrosity, which so completely obstructed the passage into the duodenum, as to admit with the greatest difficulty the finest fluid . . .'

As a rule, once a new condition has been described, fresh examples quickly follow, and since this did not occur, it might, therefore, be argued that during the eighteenth century this condition must have been exceedingly rare. A consideration of the above records suggests that such a deduction cannot reasonably be made, for, with the exception possibly of George Armstrong, whose case bears little resemblance to one of pyloric stenosis, these cases have been reported by people of little or no eminence, in journals of small circulation in the medical world, and may well have failed to attract notice. It is, moreover, remarkable that, with the exception of Weber's case, each autopsy (and, in every case, the diagnosis appears to have been made at autopsy), presents certain anomalous features that contrast with the general uniformity of the findings of the more recent cases.

Though the following case of vomiting ascribed to pyloric stenosis is advanced with considerable diffidence, for the child recovered under treatment and there could be no post-mortem confirmation, it has this interest, that it occurred in the practice of one of the foremost clinicians of the period concerned, was recorded at length in a book widely read by his contemporaries and juniors, and as we shall show excited a certain amount of attention; this case is moreover almost a hundred years prior to any hitherto described.

Fabricius Hildanus[10] was born in 1560 and died in 1634, ' full of honors and greatly beloved by all who knew him,' having practised medicine in Cologne, in Geneva, Lausanne and Berne. Dezeimeris[11], who gives a list of all the chapter headings of his concilia, regarded him as the restorer of German surgery, and his works as being even then, in 1828, a fecund source of instruction. They were translated into French in 1669, and his collected works went through at least four editions in 1646, 1652, 1652, and 1682. In addition to monographs on dysentery, lithotomy, gangrene, and on the ' Conservation of Health,' he published from time to time six ' centuries ' of clinical observations, embodied not infrequently in personal letters to his colleagues scattered throughout Europe. After his death a further seventh ' century ' was compiled from his and their correspondence. Smallpox and the plague appear frequently in these letters, and also cases of hydrocephaly, one being artificially contrived for the sake of begging, and many interesting cases. In a letter to Horstius brief details are given of one of the earliest cases of fœtal variola (C. IV, Obs. lv., p. 328), and in the very next observation an account of fœtal measles, while his descriptions of certain complications of smallpox in childhood, recorded ' quia non vulgare,' would seem still to be of considerable interest. In Hirsch's[12] estimation his is the first clear description of cancrum oris or noma—in his first ' century ' published in 1611 (Obs. xxx, p. 28) he gives four examples of this rare condition, all in children under the age of five—and he was one of the first of

his contemporaries to recognize and describe the condition now known as diphtheria (C. III, Obs. x, p. 192).

The following case he recorded under the heading of 'Observatio singularis de obstructione pylori.' It is taken from an observation (C. VI, Obs. xxxiv, p. 541) dealing with dangerous obstructions to the orifices of the stomach.

The lower orifice of the stomach, or pylorus, is rarely obstructed: for it is a little larger than the upper one, hence that which passes through the upper is easily thrust through the lower. Moreover the upper orifice is much exposed to the fluxes down from the head and also to the heated vapours that ascend in the acute diseases, the lower orifice is not so exposed; for all of which reasons it has only once been my fortune to witness this type of obstruction.

This was in 1627 in a small and wasted six months old child, the eldest son of Henry Otho, Esq. This child's stomach had been for several days crammed by his nurse or mother with a thick and viscid pultaceous feed, and its innate heat had proved unequal to the task of digesting this pap sufficiently for it to admit of being passed on to the intestine at the right time. Gradually the pap became packed in the stomach to such an extent that the pylorus became obstructed so that all the child swallowed he vomited up again and nothing passed through his bowel. Owing to this, the little child became so weak that those in attendance considered him to be at any moment on the point of giving up the ghost. It was at this juncture that I was called in, and by the divine grace had the good fortune to cure the child.

I will let you have the details of the remedies by which this was achieved but would first inform you how our people prepare the pap and how they cram it into their children.

They boil very pure farina of wheat or of spelt together with whole milk in a vessel until it goes into a thick and viscid pap; and in this as a rule they also mix some butter. Then the nurse or mother places the child supine on its back and with her right index finger takes up some of the pap and thrusts it into the mouth of the child; frequently, particularly when the child resists her, she thrusts it in as far as the fauces, so that willy nilly the child is forced to swallow the portion.

From this there often arises the very gravest symptoms, the still delicate stomach of the child being loaded with inspissated pap. For the stomach of these children indeed no longer receives what it desires but what the nurse thrusts into it by force. It is however obvious, is it not, if we are to make this point clearly comprehensible that we must first of all consider the mechanism of deglutition, whether it is reflex ('naturalis') or actually voluntary ('animalis'), and dependent on our volition.

There are some who maintain that deglutition is a reflex and others that it is a voluntary act; actually there is some truth in both modes of thought. For the act of mastication in the mouth, and subsequent propulsion on to the œsophagus is voluntary and dependent on our volition; while the actual descent down the œsophagus of the food from the mouth, which is carried out by the straight fibres ('fibris rectis') is reflex. And so, so long as the appetite for food is present, so long as in the first place the food has been sent to the œsophagus by voluntary action, the œsophagus by means of its straight fibres draws the food to itself and despatches it on to the stomach. When the appetite fails the attractive power of the œsophagus also fails, so much so that if food is offered it does not attract it but spues it out. Should however the nurse, as many of our people are in the habit of doing, thrust the food right down as far as the œsophagus, then the voluntary mechanism is placed out of court, the automatic action of the œsophagus comes into play, and in the way I have described will continue to gulp down the food to the point of disrupting the stomach, and this not without considerable danger, as in the case of our patient, to the child. In order to avoid this danger the food should be presented to the child and ingested by him from a spoon ('cochleare'). For by this method

so long as the natural appetite is present the voluntary mechanism will perform its function and convey the food on to the œsophagus, but when the stomach is satisfied the child will forthwith, before the pap reaches the œsophagus, spit it out.

I have wanted to make a note of these facts for the sake of nurses, and now in a few words will tell you how I set about obtaining a cure.

First of all I forbade the use of pap, or of other food prepared from bread or cooked farina and prescribed meat extracts only with which I mingled a small quantity of oil of sweet almonds.

In so far as there was very marked obstruction of the pap retained, I ordered inunctions of the hypogastric region of the abdomen with the following oils:—

R.

Ol. amygdalarum dulcium,	
Liliorum alborum ana ...	℥j
Ol. ex floribus	℥ʃs

misce.

and also had the following emollient quilt ('sacculus,' see Paré, Book xxvi, c. xxxix, p. 655), boiled in water applied hot to the hypogastrium:—

R.

Radicum altheæ	
Liliorum alborum ana ...	℥ʃs
Foliorum altheæ	
Malvæ ana	mj
Absynthii pontici	
Florum meliloti ana ...	mʃs
Seminis lini,	
Fœni græci,	
Anisi an	℥ʃs

Incidantur and contundantur omnia pro sacculis.

Since he was vomiting up everything given by the mouth and was passing nothing through the lower passages, I prescribed one or two nutrient enemata for every day, made from broth to which was added the yolk of an egg and a small quantity of mixed sugars. By the use of enemata the child was kept nourished for many days during the whole of which time he vomited up straightway whatever he was given by the mouth. By means of these remedies the child was fortunately restored to life and at the time of writing these notes, 2nd December, 1629, is alive and perfectly well. Not every obstruction, therefore, of the lower orifice of the stomach is to be considered incurable.

It could be very reasonably argued that this case represented simply an example of indigestion following over-feeding occurring in the practice of a surgeon knowing little of children; but this would not, I think, be quite fair, for a large proportion of the large practice of Hildanus appears to have been with children.

In 1618, when the smallpox was current in Basle, he states that with his own eyes he saw over 500 children die of the condition, and adds significantly that 'of those that survived not a few were left blind,' (C. VI, Obs. xiv, p. 509), and over eighty of his six 'centuries' of remarkable cases are concerned with children under the age of fifteen.

His statement that this was the only case of this nature that he had encountered is not, therefore, one that should be lightly discounted, and one that he rarely makes, but, it is interesting to note, he makes it again in connection with a case (C. V, Obs. liii, p. 442) apparently of diabetes insipidus, in a boy of seven. He points out that Galen[13] himself only met with two

examples of the condition and that it was one which he ' had only one occasion to note in the whole of the time he had spent in practice as a physician and surgeon.' This boy's thirst was such that each night he drank over 4,500 c.cm. of water—' plusquam decem libras '—not including the wine he mixed with it, and straightway voided it as urine. Still[14], who in 1924 had notes of 249 cases of pyloric stenosis, mentions only one case of diabetes insipidus, and John Thomson[15] in his text-book only two.

Whether or not Hildanus had described a case which really was one of hypertrophic pyloris stenosis (and it is singularly unfortunate that he gives us no clue when the condition started, other than that the child was apparently very wasted when he was called in at six months, and no definite indication as to how long recovery took), such a case report under such a heading would, one imagines, if sufficiently widely reported, focus the attention of clinicians on such cases of intractable vomiting and constipation in early infancy as they should happen to encounter in their practice.

But, while fresh examples of noma and of ' catarrhus suffocativus ' rapidly arose, I have been unable to find any other example of vomiting in infancy, thought to be due to pyloric obstruction, in the rather limited number of text-books of this period to which I have had access; and this, though there was ample evidence that the writings of Hildanus were not neglected. He is, perhaps, the most frequently quoted, as well as one of the most esteemed, authors of his time.

Wolfgang Hoefer[16] refers to this case, in the section of his ' Hercules Medicus ' devoted to children, in a paragraph headed pyloric obstruction. He gives a complete summary of it, declares it to be ' an affection in itself rare, and so hard of diagnosis,' and does not himself appear to have met with an example of the condition, though he was a clinician of considerable experience and incidentally one of the first to describe cretinism in Styria. This book of his went through at least three editions.

The two great 17th century collections of remarkable clinical cases of Forestus and of Schenkius, ' author of one of the most useful works that were published in medicine in the 16th century,' were both completed and published before this sixth ' century ' of Hildanus was published in 1641; but by 1665 references appear in editions of Schenkius[17] under the chapter devoted to affections of the pylorus calling attention to this case, which appears to have continued to arouse interest and comment throughout the next sixty years or so.

Both Dolaeus[18] in 1688, and the more renowned Hoffman[19] in 1740, however, emphasize the explanation put forward by Hildanus, and treat of it in the subsection of their chapter on pædiatrics particularly concerned with the use and abuse of thickened feeds, rather than in the sections devoted to vomiting in childhood; while the historical method of approach is further confused by the appearance during the eighteenth century of certain smaller books devoted entirely to pædiatrics by Harris, Armstrong, Astruc and Underwood, that are poor in references to former work, do not mention this case of Hildanus, but in two instances do give accounts of post-mortem examinations that suggest this condition. It is disconcerting to find

that Armstrong's case was associated by him during life with ' watery gripes,' and Underwood's[20] with a ' recurring blackness or discolouration of the infant.'

A further difficulty is presented by the enormous infant mortality rate of the period. Graunt's[21] well known figures suggested that ' of a hundred quick conceptions in London thirty-six die before they be six years '; Mallet's[22] figures for Geneva indicate an even higher rate of infant mortality during the 17th century in Switzerland.

Despite this I have ventured to recall this case, in the belief that it was better calculated to direct attention to clinical examples of hypertrophic pyloric stenosis than any other case published prior to the end of the 19th century; and that its failure to do so is possibly of significance, as is certainly the statement that such a case was only once met with in the practice of a great and busy physician.

Summary.

Attention is called to a case of pyloric stenosis in infancy published almost a hundred years prior to any previously reported case. While it is by no means certain that this case represents a true example of congenital hypertrophic stenosis in infancy, it is suggested that its publication, which aroused a certain amount of interest, would have sufficed to have directed attention to this condition had it been at all common at that time.

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CIRCUMSCRIBED CEREBRAL TUMOURS IN YOUNG INFANTS

BY

DOROTHY S. RUSSELL, M.D.,
Member of Scientific Staff, Medical Research Council,

and

RICHARD W. B. ELLIS, M.D., M.R.C.P.

(From the Bernhard Baron Institute of Pathology and the Children's Department, London Hospital.)

The following three cases are reported because of the rarity of intracranial tumours in young infants and because of the histological problems that have arisen from their study. They also present some interesting clinical features.

Case reports.

Case 1.—LEFT CEREBRAL GLIOMA IN A STILL-BORN INFANT. Still-born at term. The mother was 28 years of age; she had had four children who were alive and well, and no miscarriages. Pregnancy had been normal except for frequency of micturition during the later months. Strong labour pains began on May 24th, 1925. On the following day instruments were unsuccessfully applied by a private doctor. The mother was then admitted to the London Hospital under Dr. Russell Andrews; an anæsthetic was given at 11.45 a.m. on May 26th, 1925, and a 7 lb. still-born fœtus was delivered without instruments. The fœtus was in the right occipito-posterior position when the first examination was made, and in the right occipito-anterior position when delivered.

NECROPSY (S.D. 1138. 1925). A limited necropsy was carried out by a member of the gynæcological staff. The following notes only are available.

The specimen of intracranial tumour was obtained from a well developed female infant. The sutures of the skull were widely separated. There was great internal hydrocephalus. A solid spherical mass (8·5 × 7·5 × 6 cm.) occupied the left cerebral hemisphere. The cerebral cortex and white matter were reduced to a layer, in places only 0·5 cm. thick, over the surface of the tumour and could easily be separated from it. The leptomeninges appeared normal except for a few areas of hæmorrhagic staining. The outer margin of the tumour was lobulated and the cut surfaces presented a homogeneous pinkish grey or white surface resembling brain matter. The centre was occupied by closely packed capillaries, and contained both an opaque yellow patch (2 cm. in diameter) and a cavity containing blood clot.

MICROSCOPICAL EXAMINATION.—Three paraffin blocks were prepared from representative parts of the tumour. Sections were stained with hæmatoxylin and eosin, Weigert's hæmatoxylin and van Gieson's mixture, Weigert's fuchselin and neutral red, Mallory's phosphotungstic acid hæmatoxylin after treatment with Zenker's fluid, Laidlaw's method for reticulum, and Fincher's modification of Hortega's silver carbonate method for astrocytes[6]. No material had been reserved for frozen sections.

The tumour was clearly separable from the surrounding brain tissue which was compressed and not invaded by the tumour cells. In most areas it was composed

of interlacing bundles of closely packed cells supported by a scanty stroma of blood vessels (Fig. 1). The cells were remarkably uniform; they were of spindle or oat shape when seen in longitudinal section, and appeared in cross section as small circles or polygons. Their nuclei were oval or rod shaped: each had a fairly stout membrane and a delicate chromatin net of irregular mesh. The nodes were variable both in size and distribution; in many instances they were grouped near the nuclear membrane, but in others were more evenly distributed. There were from one to three small nucleoli. Many mitoses were present. The cytoplasm was moderately voluminous and contained stringy eosinophil material streaming at either pole of the nucleus into a fairly long process. These processes, in phosphotungstic acid hæmatoxylin and in silver preparations, sometimes contained delicate glial fibrils. In other places, using the same stains, an appearance of condensation was seen at the

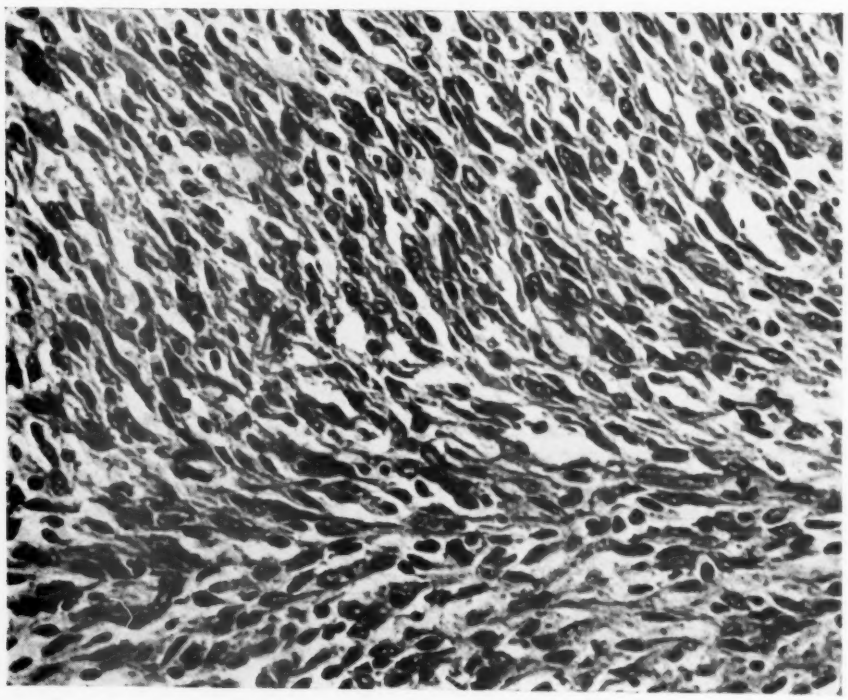

FIG. 1. Case 1.—Area showing general character of tumour. (Hæmatoxylin and eosin: × 500).

margin of the cytoplasm, forming a deeply stained tail towards the end of the process. Blepharoplasten were not present. The cells tended to ensheath blood vessels longitudinally, but were sometimes arranged at right angles to them. In many vessels an excess of endothelial cells was present.

There were many areas of degeneration and necrosis; about these a pallisading of the tumour cells was sometimes seen. Collections of amorphous hæmatoxyphil particles were present in some of the necrotic areas. With Laidlaw's method there was little reticulum in the tumour: it was confined to the blood vessels and their immediate neighbourhood.

COMMENT.—From the available data it is probable that the tumour in this case gave rise to difficulty in delivery and was therefore responsible for fœtal death. Histologically it has features that characterize it as a glioma: the reticulum was limited to the walls of blood vessels; the cells had the

appearance and arrangement of glial cells, and the fibrils present in some of them were delicate, lay definitely within the cell, and were demonstrable with silver carbonate as well as with phosphotungstic acid hæmatoxylin. Gliomata are sometimes circumscribed but are more often diffuse. The circumscribed are usually the more benign types of tumour. It is obvious, however, from the degree of cellularity and the number of mitoses that the tumour under discussion was of rapid growth. Already, in the course of intra-uterine life, it had reached an impressive size. The histological appearance was not typical of any of the commoner types of glioma. According to the character and arrangement of the cells the tumour is here regarded as a polar spongioblastoma. It is clear, however, that it has little in common with the polar spongioblastomas described by Bailey and Eisenhardt[2] and by Penfield[9], but is probably closely related to the malignant tumour of the third ventricle in a child described by Cairns and Russell[3] (Case 1 of their series) under this title.

Case 2.—PRIMARY SARCOMA OF CEREBRUM. V. H., male, aged 5 months. Full term, normal delivery, artificially fed. Parents alive and well. One sibling died from pneumonia at the age of 8 months. The infant appeared normal in every way until six days before admission to the London Hospital (March 27th, 1932). During that period he suffered from sudden attacks of projectile vomiting which bore no close relationship to feeding. The bowels were not open for five days. No other symptoms were noted; the feeds were taken well and the infant did not appear ill.

On admission the infant was well developed and nourished, weighing 14 lb. 3 oz.; the temperature was 100° F., the pulse rate 120 and the respiration rate 30. The infant reacted quite normally for his age, sitting up unsupported, grasping for objects and following a light with his eyes. He moved his limbs freely and his cry was normal. The anterior fontanelle was widely patent and bulging; the circumference of the head was $17\frac{3}{4}$ in. There was no neck rigidity and Kernig's sign was absent. The discs and fundi were normal. There was no demonstrable paralysis nor alteration of muscle tone. The knee jerks were present and equal. The reaction to pin-prick on trunk and limbs was normal. No signs of disease were found in the heart, lungs or abdomen.

On April 28th, lumbar puncture was performed. 8 cc. xanthochromic fluid, obtained under slightly increased pressure, contained 13 white cells per c.mm. with red blood cells in the stained film. No micro-organisms were seen. Protein 0·15 per cent. Wassermann reaction negative. On May 1st lumbar puncture was repeated: the fluid showed 32 white cells per c.mm. (mononuclears predominating) with many red cells. Right ventricular puncture gave 3 to 4 c.c. xanthochromic fluid under increased pressure, followed by fluid containing fresh blood. Left ventricular puncture gave 20 c.c. clear fluid under considerably increased pressure showing no deposit of blood on standing, 2 lymphocytes per c.mm., protein 0·065 per cent. Repeated ventricular punctures continued to show xanthochromic or blood-stained fluid from the right, and clear fluid under increased pressure from the left ventricle, the latter becoming blood-stained in the last puncture before death.

Projectile vomiting continued irregularly during 7 days in hospital and the temperature rose irregularly to 104° on May 3rd, 1932, the day before death. Head retraction and coarse lateral nystagmus were noted two days after admission, and the general condition deteriorated very rapidly from this time, the infant ceasing entirely to respond to pin-prick or to light. The limbs became progressively more spastic, and there were frequent clonic movements of the right arm. The patient died in coma on May 4th, 13 days from the onset of the first symptom. Repeated examinations of the discs before death showed no papillœdema. A clinical diagnosis of internal hydrocephalus and cerebral hæmorrhage, ? cerebral tumour, was made.

SUMMARY OF NECROPSY (P.M. 197. 1932). Internal hydrocephalus: primary intracranial endothelio-sarcoma. A slightly wasted male infant with sunken eyes. Foramen ovale patent to probe. Œdema of lungs. Irregular pale grey area (2 cm. diam.) in posterior border of lower lobe of left lung. Moderate parenchymatous degeneration of liver and of kidneys. Slight œdema of spleen. Mucous catarrh of dilated stomach. Focal dilatation (6 cm. circumf.) of colon. Well developed glandular thymus. Middle ears clean.

WEIGHTS (in grammes): Heart, 28·4; liver, 177·2; kidneys, 42·5; spleen, 7·1; brain, 843·4; suprarenal bodies, 4·1; pituitary gland, 0·125; thyroid gland, 0·95; thymus, 6·3; pancreas, 4·9.

MACROSCOPIC EXAMINATION OF BRAIN (after hardening in formaldehyde). The cerebral convolutions were greatly flattened. On the right there was a diffuse area of bluish discoloration involving the angular and lower part of

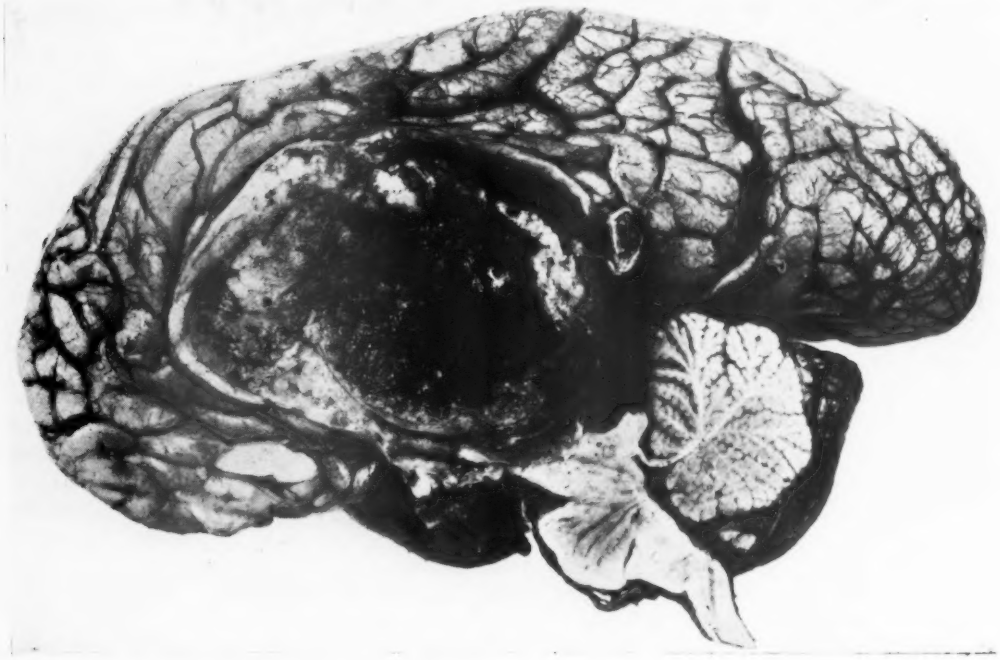

FIG. 2. Case 2. —Rightside of brain to show size and position of tumour.

the post-central convolutions. A firm, sharply circumscribed tumour (6·5 cm. from before backwards, by 4·5 cm. from above downwards, by about 6·5 cm. from side to side) occupied the centre of the brain, lying slightly more to the right than the left (Fig. 2). It replaced the lower border of the genu and anterior half of the corpus callosum, the septum lucidum and fornix, extending on the right to involve the head of the caudate nucleus, optic thalamus and mesial part of the right corona radiata. The tumour bulged down into and greatly expanded the cavity of the third ventricle, and appeared to obstruct completely the foramina of Monro. It occluded and expanded the body and all except the extreme tip of the anterior horn of the right lateral ventricle. The choroid plexus of this ventricle was incorporated with the growth anteriorly, but appeared normal elsewhere. The posterior and descending horns of the ventricle were enormously distended. On the left the basal ganglia were hollowed out to form a bed for the left border of the tumour, and the mesial surface of the left frontal lobe was concave to accommodate the bulging opposing surface of the right frontal lobe and the underlying tumour. The left ventricle also

was distended, but to a less extent than the right. The corpora quadrigemina and pineal body were flattened and distorted beneath the posterior border of the tumour.

The outer surface of the tumour was greyish white, opaque and rather friable. The cut surfaces were variegated. The greater part was greyish white, slightly translucent and finely granular. There were many small, poorly defined areas (up to 0·4 cm. diam.) of reddish-brown hæmorrhage near the periphery, and near the centre was a larger area (3·5 cm. diam.) of hæmorrhage and necrosis. In the centre of the portion in the right anterior horn was a diffuse area (1·5 cm. diam.) of slaty-grey fibrosis, streaked in places with opaque yellow, and a few small cystic areas (up to 1·5 by 0·8 cm.) with glairy contents.

The spinal cord appeared normal except for slight brown hæmorrhagic staining of the arachnoid membrane and pia. In the upper part of the sixth thoracic segment was an ill-defined area (0·25 cm.) of grey pearly thickening of the pia adjacent to the right posterior root.

MICROSCOPICAL EXAMINATION.—Paraffin sections were prepared from three blocks

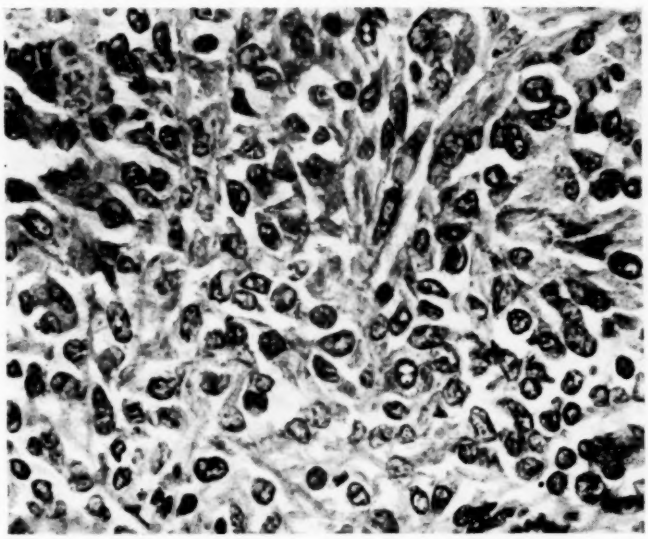

FIG. 3. Case 2.—Area to show general character of tumour. (Hæmatoxylin and eosin ; × 300).

taken from representative parts of the tumour, and from the sixth thoracic segment of the spinal cord. A fourth block of the tumour was used for frozen sections. Paraffin sections were stained by the methods already enumerated with the addition of Bielschowsky's method (Davenport's modification) for neurofibrils. Sections cut on the freezing microtome were stained with Scharlach R and hæmatoxylin, by Penfield's modification of Hortega's method for oligodendroglia and Cajal's gold chloride sublimate method for astrocytes. Spare sections were also stained by Hortega's method for astrocytes after storage for a fortnight in formol-bromide.

In most places the tumour was clearly separable from the adjacent brain. Both frontal cortex and ependyma were compressed and stretched over it and evidence of invasion was restricted to a few places in which ependyma and subependymal glia were replaced by tumour tissue.

Most of the tumour cells were round or polygonal, and were arranged loosely in acini of various sizes separated by a scanty stroma of blood vessels (Fig. 3). The cells varied considerably in size. They had a fairly abundant, faintly eosinphil

vacuolated cytoplasm and a relatively large round or oval nucleus, which was often indented in one or more places and was occasionally cup-shaped. The nuclear membrane was moderately stout and well defined, the nucleoplasm pale and clear and traversed by an exceedingly delicate chromatin net beset with a very few small nodes. One or two large nucleoli lay near the centre. Many mitotic figures were present. These cells had no demonstrable affinity for either gold or silver when stained by the methods mentioned.

With Laidlaw's stain for reticulum, a conspicuous network of delicate fibrils enclosing small groups of cells was found, particularly near the anterior margin of the tumour (Fig. 4). This reticulum was not accounted for by any extra vascularity or organization of the tissue in the regions where it was most abundant. In other parts of the tumour it was less abundant although everywhere there was more than is usually encountered in gliomas.

Slight variations in structure were demonstrated in different parts of the tumour.

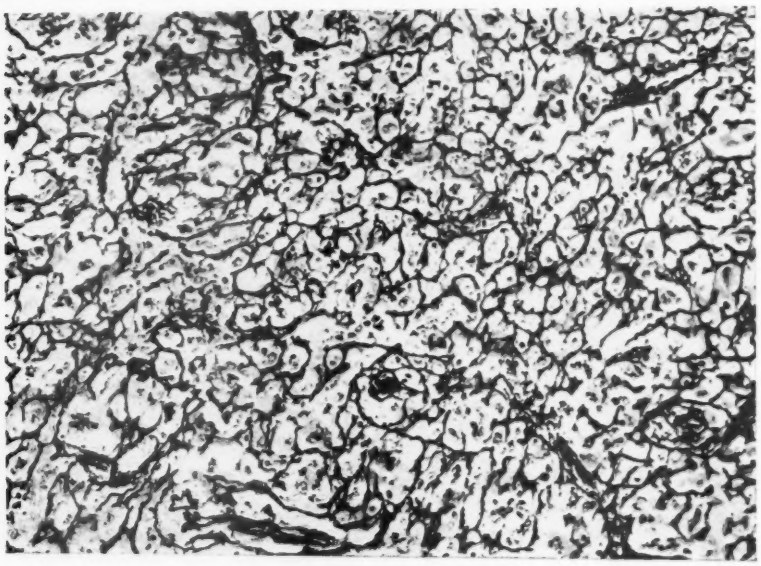

FIG 4. Case 2.—Area in anterior part of tumour showing distribution of reticulum. (Laidlaw: × 110).

Thus, in the anterior part, where reticulum was most abundant, the cells were arranged in small syncytial groups or short trabeculæ separated by an œdematous stroma of collagen and reticulum (Fig. 5). In this area mitoses were conspicuous. Near the ventricle the cells were closely packed and occasional strands of elongated spindle cells were present. Within the cytoplasm of these one or two delicate fibrils were sometimes seen with phosphotungstic acid hæmatoxylin. Also in the neighbourhood of the ependyma was seen an area in which there was a conspicuous perithelial arrangement of the tumour cells round small blood vessels. Here too mitoses were conspicuous.

Large areas of hæmorrhage and smaller foci of degeneration and necrosis were scattered throughout the tumour; in these necrotic areas were collections of extracellular fatty material and fat granule cells which corresponded, in silver preparations, to the distribution of amœboid microglia.

In the sixth thoracic segment there was a crescentric area of infiltration by polygonal tumour cells in the pia over the right posterior column and adjacent root. The cells were loosely packed and were supported by a considerable stroma of thin collagen fibrils. The adjacent spinal cord appeared normal.

LUNG.—In pale grey area in the posterior border of the lowest lobe of the left lung the alveoli were crowded with large foamy macrophages. A few similar cells were present in the lumina of the respiratory bronchioles and in some of the smaller bronchi. There was but little focal inflammatory infiltration of the interstitial tissue consisting of large lymphocytes and a few neutrophil leucocytes. Occasional collections of bacteria in alveoli and bronchioles were not associated with any cellular reaction. The histological picture was not that of a pneumonia; it might possibly have been accounted for by the inhalation of a small quantity of milk.

COMMENT.—Owing to the extreme readiness with which separation of the cranial sutures and expansion of the anterior fontanelle can occur in early infancy, the signs and symptoms of intracranial tumour at this age are liable to differ somewhat from those observed when the condition arises after the skull has become more rigid. This is well illustrated by the present case.

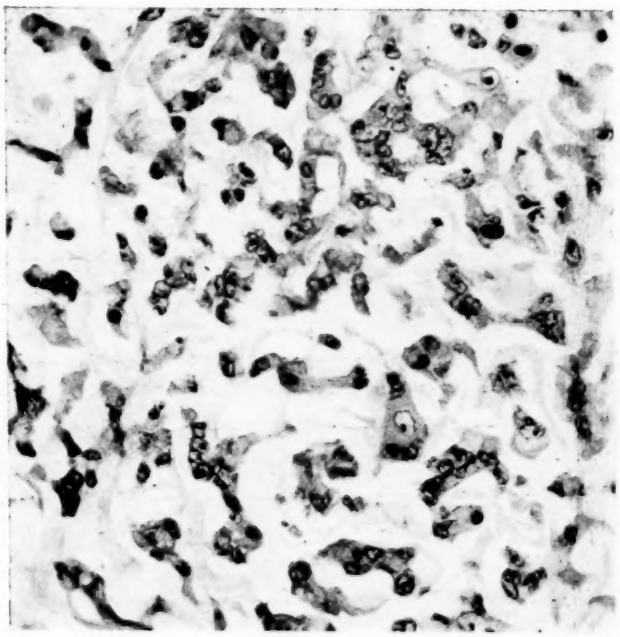

FIG. 5. Case 2.—Area in anterior part of tumour showing cells in syncytial groups and short trabeculæ. (Hæmatoxylin and eosin : × 275).

Although the tumour was probably of rapid growth the extremely short history and paucity of signs until a terminal stage had been reached are remarkable in view of the large size of the growth. Thus the presenting symptom was projectile vomiting of cerebral type which occurred for the first time thirteen days before death. When the infant was first seen, six days after the onset of the vomiting, the only physical signs of disease were bulging of the anterior fontanelle and an increase in the circumference of the skull to three-quarters of an inch in excess of the average for the age. Papillœdema was absent up to the time of death, and though this sign is not a constant finding with intracranial tumours, especially with those

above the tentorium, even at a later age, its entire absence with a tumour of this size is exceptional. Clinical deterioration was rapid after the first symptoms were observed.

The presence of internal hydrocephalus of obstructive type was shown before death by obtaining repeated samples of ventricular fluid under increased pressure. That the obstruction involved the foramina of Monro was demonstrated by the dissimilarity in the specimens obtained from the two ventricles: the fluid from the left ventricle was clear whereas the right ventricular and lumbar fluid was xanthochromic or blood-stained. These clinical observations were confirmed by post-mortem examination. The xanthochromia of the fluid in the right ventricle and spinal canal was probably the result of independent hæmorrhages into the lateral and third ventricles respectively. The observation of hæmorrhagic staining of the spinal meninges supports this explanation.

The appearance, arrangement and staining reactions of the cells in the intracranial tumour in this case and the amount of reticulum present rule out the possibility that it is a glioma. The lack of any specific differentiation on the part of the tumour cells, however, makes it difficult to name. There is no evidence that it is a teratoma. The pineal body was intact. The relative abundance of reticulum suggests that it is a tumour of mesodermal origin. If so, it must be regarded as originating from the tela choroidea, or from the stroma of one of the choroid plexuses, or from the perivascular sheath of one of the perforating vessels. Inasmuch as all these structures are derived from the pia it would be correct to regard the tumour as a malignant endothelioma or sarcoma. An alternative possibility that the tumour is a carcinoma of the choroid plexus must also be considered. In support of this is the conspicuous perithelial arrangement of the cells about a central vascular core in one part of the tumour, the patchy distribution of reticulum and lastly the tendency of the reticulum fibrils to enclose groups rather than individual cells. In secondary carcinoma of the brain the amount of reticulum is exceedingly variable even if the different specimens examined are derived from the same type of primary tumour, for example carcinoma of the lung. In one specimen of this type the amount of reticulum present in the metastasis was considerable, even though remote from the meninges, and was comparable to that observed in this tumour. The reticulum in the metastasis, however, could be attributed to the proliferation of spindle fibroblasts amongst the tumour cells, whereas in the tumour under discussion a cellular stroma of this kind could not be detected. It must be concluded therefore that the reticulum was produced by the activity of the tumour cells.

Thus in the light of the available evidence it is reasonable to regard this tumour as a primary sarcoma or malignant endothelioma of pial origin. The focus of tumour cells in the pia of the thoracic spinal cord was interpreted as a metastasis from the main tumour. Such metastases are of frequent occurrence in all the commonly recognized kinds of glioma[3], but have not previously been recorded in circumscribed tumours of this kind. The

presence of these metastases in the spinal canal depends less upon the intrinsic malignancy of the primary tumour than upon the close contiguity of the tumour to the subarachnoid cerebro-spinal pathway.

Case 3.—PRIMARY SARCOMA OF CEREBRUM. K. B., male, aged 1 year 11 months. The infant, an only child, was born at term after a prolonged labour and weighed 10½ lbs. He was breast fed for 10 months and apart from pertussis at 1 year was quite well and developed normally up to the age of 1 year and 8 months (Dec. 31st, 1932). At this time there was vomiting of sudden onset which occurred each morning for two weeks and then ceased. The child then developed a divergent strabismus of the left eye for which glasses were prescribed at an eye hospital. The general condition was good until one month before death, when the child was suddenly

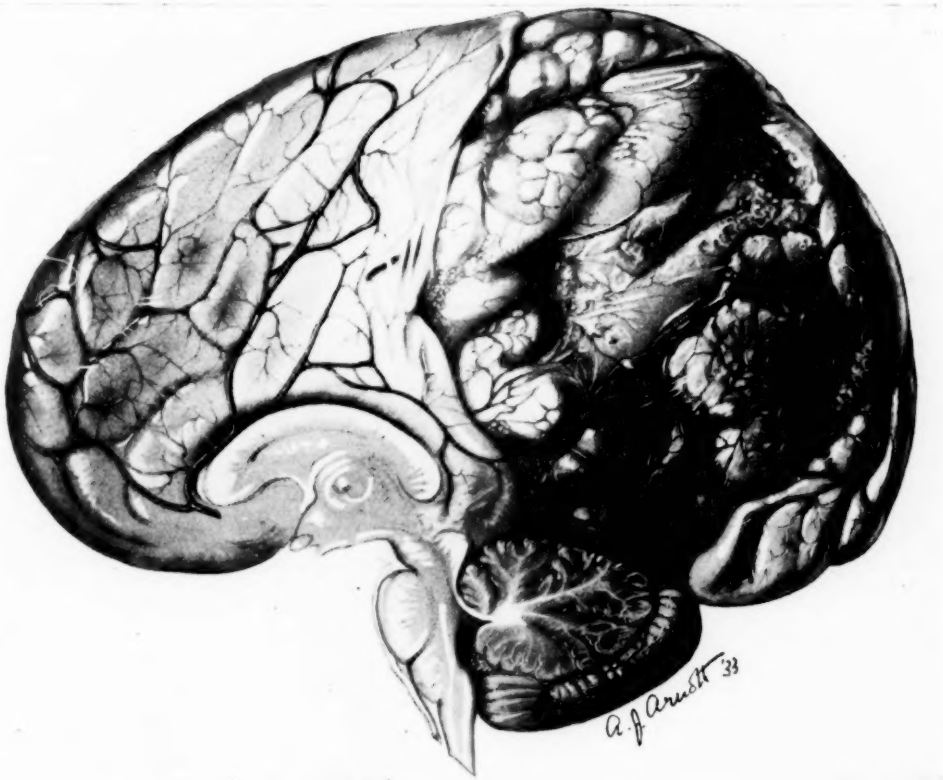

FIG. 6. Case 3.—Mesial aspect of right hemisphere showing tumour in parieto-occipital region.

unable to sit up or walk and became increasingly drowsy. There was loss of appetite and constipation for two weeks.

On March 16th, 1933, the child was admitted to the Hospital for Sick Children, Great Ormond Street, under Dr. Frew. He was drowsy and irritable when roused. He continually rubbed his nose. The general nutrition and development was good. The head was obviously enlarged with separation of the sutures and a circumference of 21½ in. The scalp veins were dilated especially over the left temple. Both discs appeared pale and the margins definitely blurred; there was some engorgement of the vessels, with marked congestion around the discs. The pupils were central, but reacted very sluggishly to light. There was a slight divergent strabismus of the

left eye. The arm jerks were normal; the abdominal reflexes and the knee and ankle jerks were not obtained. Extensor plantar reflexes were obtained on both sides. The pulse rate was 120 and the volume good. The blood pressure was 110/45. There were scattered râles in both lungs posteriorly, but no other physical signs of disease. Lumbar puncture (March 18th) yielded clear fluid of normal composition under increased pressure.

The infant became comatose on the day following admission and showed slight spasticity of the left arm. The temperature rose to 104° and the pulse rate to 160; there was appreciable increase in the circumference of the skull. Death occurred on the fourth day in hospital. A clinical diagnosis of cerebral tumour was made.

NECROPSY.—We are indebted to Dr. R. C. Lightwood for the following note:—

A fairly nourished infant with considerable degree of post-mortem change. Cranial sutures wide with no erosion of bones of skull. Flecks of calcareous deposit in dura over vertex and at base. No hydrocephalus. Liver fatty. Spleen, heart, lungs, kidneys and suprarenals, post-mortem changes only. Weights: body, 11·34 kgrm. (length 94 cm.); heart, 60; liver, 200; spleen, 35; kidneys, 32 grm.

The right half of the brain was received after hardening in formaldehyde. The posterior half of the right cerebral hemisphere was replaced by a hard globular growth (7 cm. from side to side, by 11·3 cm. from before backwards, by 10 cm. from above downwards). This presented a flat nodular surface (9·5 by 10 cm.) beneath the leptomeninges covering the mesial surface of the parieto-occipital lobe (Fig. 6). Here the brain tissue had almost entirely disappeared but could occasionally be identified as a thin translucent layer between the meninges and the surface of the tumour. Anteriorly the brain formed a sharp crescentic border round the tumour and posteriorly there was a small cap of the occipital lobe (2 cm. deep), which, however, had been almost entirely detached from the tumour. The right lateral ventricle and basal ganglia, the corpus callosum and callosal gyrus were pushed forwards and compressed. The corpora quadrigemina also were compressed into a pyramidal mass (0·9 cm. from before backwards by 0·6 cm. high). The pineal body was not present in this half of the brain.

The exposed portion of the tumour was opaque, greyish white and extremely firm. In places the texture resembled that of a cauliflower, but mostly was composed of smooth nodules and flat bosses from 0·5 to 1·5 cm. in diameter. On section, the cut surfaces were everywhere solid and extremely firm: the tissue was composed in part, and especially at the periphery, of white glistening tissue, slightly translucent. In the centre were a few areas (up to 2 cm. diam.) of lemon-tinted gelatinous material flecked with brownish-red streaks and dots. Also near the centre were a few sunken slaty grey areas of fibrosis. The greater part of the tumour was variegated with glistening white areas, similar to the peripheral zone, interspersed with more extensive diffuse grey patches of translucent appearance which were thickly beset with fine hair-like dark red streaks and dots. Most of these streaks and dots were surrounded by a narrow zone of pearly white tissue making them conspicuous to the naked eye. These grey areas were flexible and extremely firm.

MICROSCOPICAL EXAMINATION.—Representative blocks from the periphery and more central parts of the tumour were embedded in paraffin. The block from the periphery was first cut on the freezing microtome and sections were stained with Scharlach R and hæmatoxylin, by Hortega's method for pineal parenchyma, and by Penfield's modification of Hortega's silver carbonate method for oligodendroglia, and Cajal's gold chloride sublimate. The remainder of the block was then embedded in paraffin. Paraffin sections were stained by the methods already enumerated.

The tumour was markedly cellular, but varied greatly in density in different parts. The periphery was composed of closely crowded round or polygonal cells; in the deeper areas these aggregated round cells were separated into masses of varying size and shape by broad zones in which parallel spindle cells were more

sparsely arranged in an abundant fibrillar or sometimes hyaline stroma of connective tissue (Fig. 7). These strands of spindle cells broke up into thinner trabeculæ which penetrated everywhere into the collections of round cells. No sharp demarcation was found between the round and spindled celled zones: transitions existed everywhere between the two types of cell. Their nuclei also were of similar structure. In the round cells the nucleus also was round or, less commonly, lobed and had a delicate membrane and clear pale nucleoplasm traversed by an irregular net of chromatin. The chromatin content varied greatly: in some instances there were a few small nodes only, in many others the nodes were large and irregularly distributed. Many also were hyperchromatic. There were from one to three small nucleoli. The nuclei of the spindle cells were elongated but were in other respects similar.

No intra-cytoplasmic fibrils were demonstrated with phosphotungstic acid hæmatoxylin. There was, however, an abundance of fine elastic fibrils which were

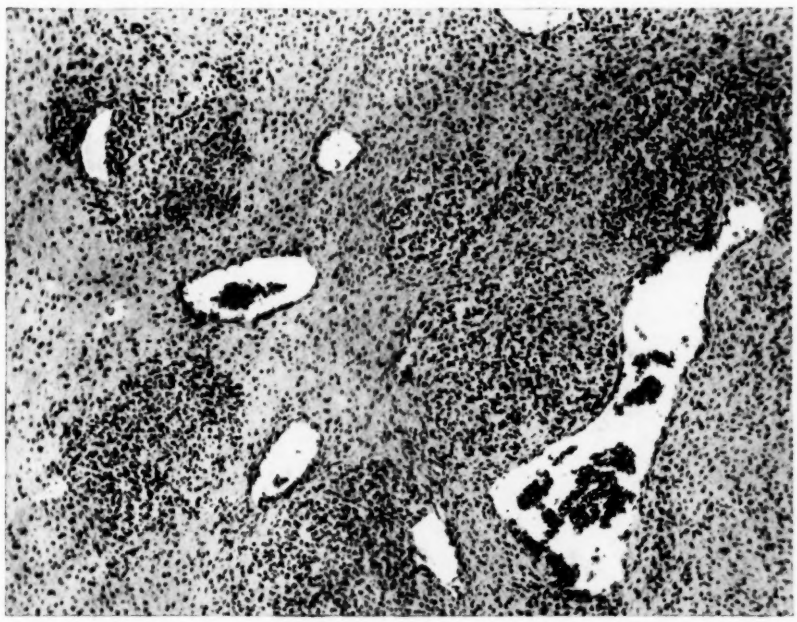

FIG. 7. Case 3.—To show general character of tumour. (Hæmatoxylin and eosin: × 85).

distributed between the spindle cells and formed a more feebly stained and often beaded intercellular net in many of the round-cell areas. With Laidlaw's method a great abundance of both fine and coarse reticulum fibrils was demonstrated. The distribution however was uneven: in the cellular peripheral zone the fibrils were scanty but they became increasingly abundant as the deeper parts were approached. They formed dense bundles in the spindle-cell areas and a pericellular net in many of the deep collections of round cells.

Irregularly shaped areas of degeneration and necrosis were present in the deeper parts. The blood vessels were sparse but are conspicuous by reason of their dilatation and engorgement.

All the metallic impregnation methods produced negative results.

COMMENT.—In this case the clinical history is again of relatively short duration though the contrast of the clinical picture with that seen in older

subjects is less striking than in Case 2. Vomiting occurred for the first time three months before death, and papillœdema was present when the child was admitted to hospital. Whereas in Cases 1 and 2 the tumour had caused a considerable degree of internal hydrocephalus, in this case there was no hydrocephalus because the tumour had not interfered with the flow of cerebrospinal fluid from the ventricles. The increase in the size of the head which occurred is to be attributed to pressure from the growth of the tumour.

Microscopically the tumour appears to be a fibrosarcoma. The naked eye appearances suggested that it might be a teratoma, but this diagnosis was not supported by the histological examination. The spindle cells in the tumour are clearly fibroblasts. They have produced an abundance of collagen, reticulum and elastic fibrils. That the round cells are of a similar nature appears certain because there are transitions between them and the spindle cells, their nuclei are of similar character and they also are frequently separated by delicate elastic and reticulum fibrils. The tissue of origin is either the cerebral leptomeninges or the pial investment of a perforating vessel. The tumour in general bears little resemblance to the meningiomata that arise from the dura mater in later life. There is, however, a conspicuous tendency for the round cells to be arranged concentrically around vessels. A further point of resemblance lies in the production of elastic fibrils. Mallory[8] found great variations in the amount of elastic produced in the dural endothelioma or, as he called it, the arachnoid fibroblastoma. He observed that in some it ' occurs as a fine to coarse reticulum which is distributed fairly evenly everywhere between the cells,' and also that ' the stain of the fibrils varies. It is intense in those which are fully developed but grades downwards to almost nothing in those which are newly formed. This variation of intensity of stain and character and distribution of the fibrils indicates that they are the product of the tumour cells.'

Discussion.

The cases here reported clearly show that progressive expansion of the skull in a young infant may in rare instances be caused by a large circumscribed tumour of the cerebrum. Such a tumour may be a glioma (Case 1), or a sarcoma (Cases 2 and 3). Teratomata may also occur in a similar situation and produce similar results[5]. The macroscopic features of such tumours suggest that early recognition of the condition followed by radical surgical treatment might be of benefit to the patient. Unfortunately the readiness with which the expansile skull of the infant compensates for raised intracranial pressure may result in the condition being far advanced before the patient comes under medical observation. Moreover, the impossibility of making a full neurological examination in young infants increases the difficulty of reaching an accurate diagnosis.

The histological problems raised by these cases have already received comment. In Case 1 the tumour is a glioma and has been called a polar spongioblastoma. Although it appears to be recognized[7] that gliomata may

occur in the new born, we have no personal knowledge of any detailed description of such a tumour. That reported here is the sole example of its kind in a series of 358 intracranial gliomata examined in this laboratory. The incidence and topography of gliomata in the early years of life has been described by Cushing[1]. It is generally agreed that they are commoner below the tentorium than above in children under 15 years. Our own figures agree fairly well with those of Cushing. Thus 55 of our total of 358 gliomata were in subjects of 15 years or under. Of these 12 only were situated in the cerebral hemispheres. The distribution in the different age groups is as follows: below 1 year, 1 cerebral (Case 1) and 2 subtentorial; 1–5 years, 1 cerebral and 8 subtentorial; 5–10 years, 4 cerebral and 19 subtentorial; 10–15 years, 6 cerebral and 12 subtentorial. In two cases, omitted from this analysis, there was a diffuse gliomatosis of the leptomeninges without any demonstrable primary tumour.

The tumours in Cases 2 and 3 are not gliomatous: they probably have arisen from the pia and are sarcomatous. In Case 3 there is more certainty in reaching this conclusion than in Case 2: fibroblasts undoubtedly are the type cell of the tumour in Case 3. In the tumour of Case 2 the cells are endothelioid rather than fibroblastic in character. But as the primary tumours of the dura mater in older subjects show even greater divergence in histological structure, it cannot be considered that the dissimilarity of the tumours in Cases 2 and 3 in any way invalidates our conclusions concerning their nature.

The occurrence of these circumscribed sarcomata of the brain has already been demonstrated by Bailey[1]. In certain of his cases, however, the possibility that the intracranial tumour was metastatic could not be dismissed because the necropsy was limited to an examination of the head. In our two cases this possibility can be dismissed. This kind of tumour has also been commented upon recently by Cushing[2]. He reaffirms that, apart from a true diffuse sarcomatosis of the meninges in childhood, there are also circumscribed enucleable tumours that should be regarded as sarcomatous. It is remarkable, however, that these tumours can be removed without subsequent recurrence of the growth, a circumstance that belies their malignant histological appearance. Undoubtedly, as Cushing observes, this kind of tumour deserves further study.

Summary.

1. Three circumscribed tumours of the cerebrum occurring in early infancy are reported from both clinical and pathological aspects.

2. Attention is drawn to the modification of the clinical picture which may occur from the readiness with which the skull expands at this period when the intracranial pressure is raised. In general, the clinical history tends to be of short duration and deterioration is rapid after the infant first comes under observation.

3. The tumour in the still-born infant in Case 1 is a glioma: a polar spongioblastoma. In Cases 2 and 3 the tumours are both regarded as sarcomata of pial origin. This diagnosis appears certain in Case 3, but is tentative in Case 2.

It is a pleasure to thank Doctors Russell Andrews, Maitland-Jones and Frew for permission to use the clinical notes of the cases under their care. We also thank Professor H. M. Turnbull and Mr. Hugh Cairns for their help and criticism in the preparation of this paper.

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A CASE OF AMYOPLASIA CONGENITA, WITH PATHOLOGICAL REPORT

BY

DOROTHY STOPFORD PRICE, M.B.
Physician to St. Ultan's Infant Hospital, Dublin.
Clinical Assistant (Children), Royal City of Dublin Hospital.

This communication presents a record of the investigations made in a case of amyoplasia congenita (arthrogryposis multiplex congenita, multiple congenital articular rigidity).

Clinical report.

A female infant, aged six weeks, was referred to St. Ultan's Hospital, Dublin, on April 14th, 1932, by Dr. O'Donoghue of Aunascaul, Co. Kerry. She was the eighth child of healthy parents, all the children being alive and well. There was no history of ill-health or deformity on either side of the family, nor of intermarriage. The birth was a normal vertex presentation, and the midwife noticed that there was little or no amniotic fluid. The condition at 6 weeks showed a well-nourished female child weighing 8½ lb. (Fig. 1 and 2 show her at 4½ months.)

The arms showed no voluntary movement at the shoulders or elbows. The elbows appeared thickened and spindle-shaped. The left elbow joint could be flexed with difficulty to a right angle, and there was only slight flexion in the right. The hands lay in a position of congenital club hand with ulnar deviation; the wrists were flexed and could not be fully extended; the finger joints were flexed with the fingers partially overlapping each other and slightly webbed. The fingers could be separated and extended with difficulty. The skin on the palmar surfaces was tight and contracted. The legs were everted and stiff. The eversion could be corrected, but correction was impeded by spasm. The thighs lay in a position of coxa vara, and sometimes in scissor position, with thighs everted. There was some thickening of the knee joints, but the knees could be flexed and extended passively. The spine was held straight and rigid. This was due to spasm and disappeared later. The chest was normal except that the neck muscles appeared weak.

X-ray examination by Dr. McDonogh showed bilateral dislocation of the hips. No other bony deformity was observed. The diminished muscle shadow showed in the X-ray of the upper limb (Fig. 3).

On the advice of Mr. Arthur Chance, the hands were put up in plaster casts, remoulded once a week to an improved position, and removed daily for massage and exercises. As the position of the hands improved the whole upper limb was put up in the same way, with increasing degrees of flexion at the elbow, and still with daily movements and massage. The trunk, shoulder, neck and leg muscles were also massaged.

After 3 months treatment, on the publication of Dr. Sheldon's case[1], the faradic reaction of muscles was tested. Owing to difficulties due to the size and age of the patient, it was felt at the time that the findings might be unreliable, and the subsequent dissection of the arm proved this to be the case. At this stage, at the age of 4½ months, the condition was as follows:—The child could raise both arms from the shoulders, apparently by lifting the scapulæ; there was some degree of rotatory movement of the arms; no voluntary flexion of the elbow joints; the hands had opened up, the fingers spread, and the wrists had assumed a normal position though they tended to relapse if the splints were left off for long. The child could

hesitatingly reach up and grasp a pencil held horizontally above her. Her intelligence was remarkable. The legs had loosened out and she was beginning to kick. The head was not held up as well as is normal at 4½ months, but tended to fall forwards. The spasm causing rigidity of the spine had disappeared. The child developed a severe attack of enteritis at 5 months, terminating in an intussusception, and died on July 24th, 1932.

FIG. 1. Patient aged 4½ months.

Post mortem examination.

The body of a well-nourished infant, with the limbs in characteristic attitude, arms rotated in, elbows extended, wrists and fingers flexed. The skull was thin, the anterior fontanelle measured 2½ by 3 inches. The dura was adherent to the skull, but the brain was apparently normal. The pituitary was removed. From the abdomen the spleen, right suprarenal and right kidney were removed. The small intestine was generally rather congested, and showed an intussusception of the ileum into ascending colon, the entering layer being deeply congested. Portions of quadriceps femoris and glutæus maximus were removed. The right sterno-clavicular joint was disarticulated and the right upper limb removed. The sterno-mastoid muscles appeared well developed. The spinal cord was removed from 4th cervical to 4th thoracic segments. The thymus gland was enlarged.

FIG. 2. Patient aged 4½ months.

FIG. 3. Skiagram showing congenital dislocation of hips and diminished muscle shadow in upper limb.

Report on dissection of elbow joint.—(Dr. C. P. Martin and Mr. E. B. McEntee).—The skin was normal. The elbow joint was slightly flexed, the arm and forearm forming an angle of 150 degrees. It could be moved, with difficulty, through an angle of 15 degrees. The forearm was pronated, the wrist flexed and slightly adducted. The fingers were flexed and the thumb drawn across the palm.

On dissection the superficial fascia was abundant. It presented two well defined bands, one lying over the biceps the other over the brachioradialis. From their composition and attachments it was evident that they could not limit flexion of the elbow joint. Each was composed of loose fat covered by a layer of fascia. That over the biceps was attached above to the coracobrachialis, below to the tendon of biceps. The second band extended from the lateral supracondylar ridge of the humerus to the distal end of the radius, covering the brachioradialis and the lateral border of the forearm. It was smooth, rounded, and attached to the deep fascia on the volar and dorsal aspects by its fascial sheath.

1. MUSCLES CONNECTING THE ARM WITH THE VERTEBRAL COLUMN.—The trapezius, latissimus dorsi, rhomboid major and rhomboid minor were normal; and the levator scapulæ was not available.

2. MUSCLES CONNECTING THE ARM TO THE ANTERIOR AND LATERAL THORACIC WALLS.—The pectoralis major, pectoralis minor, and serratus anterior were normal; and the subclavius not available.

3. MUSCLES OF THE SHOULDER.—The deltoid was greatly reduced in size. The origin from the lower lip of the spine of the scapula was very small. Cleaning and definition of the muscle was made difficult by the presence of fibro-fatty material between the muscle bundles. The subscapularis, supraspinatus, infraspinatus, teres major, and teres minor were all normal.

4. MUSCLES OF THE ARM.—The coracobrachialis and triceps brachii were normal. The biceps brachii was covered by the fatty band mentioned above. When the band was dissected away the muscle was found to be very slender. The short head was tendinous and small, the long head constituting the greater bulk of the muscle. The brachialis was almost entirely replaced by fibro-fatty material. A small bundle of muscle fibres was present along the lateral and posterior part.

5. MUSCLES OF THE FOREARM.—In the superficial group of the volar antibrachial muscles, the pronator teres, flexor carpi radialis, palmaris longus, flexor carpi ulnaris, and the flexor digitorum sublimis were normal. In the deep group the flexor pollicis longus, flexor digitorum profundus and the pronator quadratus were normal.

In the superficial group of the dorsal antibrachial muscles the brachioradialis was reduced in size, especially in its upper portion; the extensor carpi radialis longus was reduced in size; the extensor carpi radialis brevis was absent or so small that it could not be seen with the naked eye; and the extensor digitorum communis, extensor digiti quinti proprius, extensor carpi ulnaris, and the anconæus were normal. In the deep group, the supinator was normal; abductor pollicis longus showed a radial head which was slender and fatty; the extensor pollicis brevis was very slender; and the extensor pollicis longus, and extensor indicis proprius were normal.

SYNOPSIS OF ABNORMAL MUSCLES. 1. Absent:—extensor carpi radialis brevis. 2. Reduced in size:—biceps, brachioradialis, extensor carpi radialis longus, and extensor pollicis brevis. 3. Reduced in size, plus fatty changes:—deltoid, brachialis, and radial head of abductor pollicis longus.

When the muscles were dissected off the range of movement of the joint was increased by 5 degrees. The lower end of the humerus was straight, and from the front presented a fulness instead of the usual radial and coronoid fossæ. The radial collateral ligament was strong and well defined. A strong band of fibrous tissue extended from the lateral epicondyle of the humerus to the posterior border of the ulna below the lesser sigmoid notch. This band was tightened on flexion and

appeared to limit this movement. The ulnar collateral ligament was very strong. The posterior portion, normally triangular, was quadrilateral, the upper margin being attached to the medial epicondyle and the posterior part of the shaft of the humerus.

The exposed portion of the capsule appeared normal. When the joint cavity was opened the articular surfaces on the lower end of the humerus were found to be abnormal (Fig. 4). The trochlea and capitulum were confined to the inferior surface and did not extend, as in the normal, on to the front of the bone. On the

FIG. 4. Anterior aspect of lower end of humerus. Note that capitulum and trochlea do not extend on to the anterior aspect of the bone. The bone is full and convex where normally the radial and coronoid fossæ are situated.

upper part of the greater sigmoid notch, that formed by the olecranon, the articular cartilage was replaced by fibrous tissue which was attached to the olecranon fossa just above the margin of the trochlea. When this band was cut the joint could be fully flexed.

In the wrist joint the interosseous ligament between the proximal ends of the lunate and triquetrum was attached to the articular surface of the radius thus separating the radio-lunate from the radio-triquetral portion. The shoulder joint appeared normal.

With regard to the question whether the disease is primary in the joints or in the muscles it can only be remarked that if the condition in the joint is primary it is very difficult to account for the distribution of the changes in the muscles.

Report on microscopic sections.—The thymus, spleen, kidney, and pituitary and pineal glands were normal in appearance. The muscle sections were stained with hæmatoxylin and eosin, and with Heidenhain Azan stain. The quadriceps extensor and glutæus maximus showed some degree of degeneration of muscle fibre. The flexors of the arm showed the same degenerative changes, but more widespread. The brachialis was the most degenerated, biceps next, and deltoid least. The muscle sections showed striated muscle fibres, areas of fibrous tissue, and fat replacement. There were also some infrequent zones of small atrophied fibres and chains of nuclei with degenerated sheaths. No myoblasts were seen in these sections (Fig. 5).

Report on spinal cord (Dr. R. J. Gladstone).—The specimens stained with hæmatoxylin and eosin, and by van Gieson's method, showed considerable shrinkage of the nerve cells. Both grey and white matter were feebly stained with eosin and

FIG. 5. Longitudinal section of the deltoid showing striated fibres, atrophied fibres and fat (× 120).

the nuclei were unstained with the hæmatoxylin. The ependymal lining of the central canal of the spinal cord was complete and well stained. The canal was slightly larger than normal, the diameter being 0·12 mm. A large U-shaped space was present in the central part of the grey matter; the bend of the U was in the anterior grey commissure and the two limbs passed dorsally one on each side of the central canal. Sections of several small vessels were seen in the space and appeared to lie free in the cavity, the surrounding and supporting and nerve tissues having disappeared. Other smaller spaces and fissures were present both in the grey and white matter.

Small yellow and black particles were scattered sparsely through the section. These were present in both grey and white matter, and also in sections of the ventral

and dorsal roots of the spinal nerves which lay in the subarachnoid space around the cord. The yellow particles appeared to be degenerate red blood corpuscles.

The multipolar ganglion cells in both the anterior and posterior cornua of the grey matter were shrunken and degenerate (Fig. 6). The cells of the anterior cornua were less affected on one side than the other. The nuclei of these cells were either unstained or feebly stained with the hæmatoxylin.

The white columns as a whole appeared degenerate, the outlines of the nerve fibres being almost indistinguishable. The tissue consisted chiefly of a fine neuroglial network traversed by blood vessels which appeared to radiate from the grey matter, and, owing to the degenerate condition of the nerve fibres, were unusually distinct. Owing to the general condition of degeneration of the nerve fibres, no specially degenerated tracts were indicated by the Marchi method; the fibres of the crossed pyramidal tract were more darkly stained by this method than the dorsal spino-cerebellar tracts, and the cross section of the nerve fibres of the pyramidal tracts

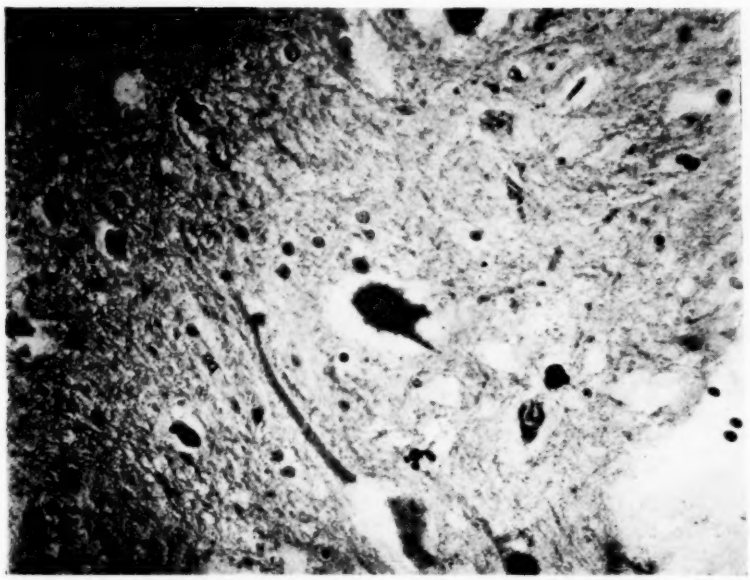

Fig. 6. Section of cord showing cells of anterior horn. Stained H. and E. (× 320).

appeared slightly more distinct than in the spino-cerebellar tracts. The antero-median columns of white matter were much distorted and reduced in the antero-posterior diameter. The grey matter of the dorsal cornua appeared to be broken up, and to consist chiefly of neuroglial fibres.

Transverse sections of the roots of spinal nerves in the subarachnoid space showed nerve fibres which for the most part were feebly stained by the Marchi method (Fig. 7). In the sections stained by van Gieson's method some nerve fibres showed a thin sheath completely stained and appearing as a black ring; in others only a part of the circumference was stained, the clear area in the centre being bounded on one side by a dark semi-circle or crescent, the remainder of the sheath being unstained.

The pia arachnoid and the dura mater were thickened, and the connective tissue fibres were well stained by both the hæmatoxylin and eosin and the van Gieson stains. The pia was very vascular. The thickening of the dura mater and increased vascularity of the pia mater appeared to be the result of a chronic inflammatory condition of the membranes.

Discussion.

Previous writers on this condition have directed their attention mainly to the joint condition, and the disease became known as arthrogryposis multiplex congenita. Scarlini[2] suggested that the cause was muscular ligamentous retraction. Stern[3] regarded the condition as due to a rare combination of intra-uterine peri-arthritis and intra-uterine pressure. Rocher[4] considered that compression in utero affected all tissues equally. W. Sheldon was the first to put forward the hypothesis that the muscles were primarily at fault. His investigations on the electrical reactions of the affected muscles confirmed this view. After quoting the literature and adding notes on four cases of Fairbank's besides his own, he put forward the view that the

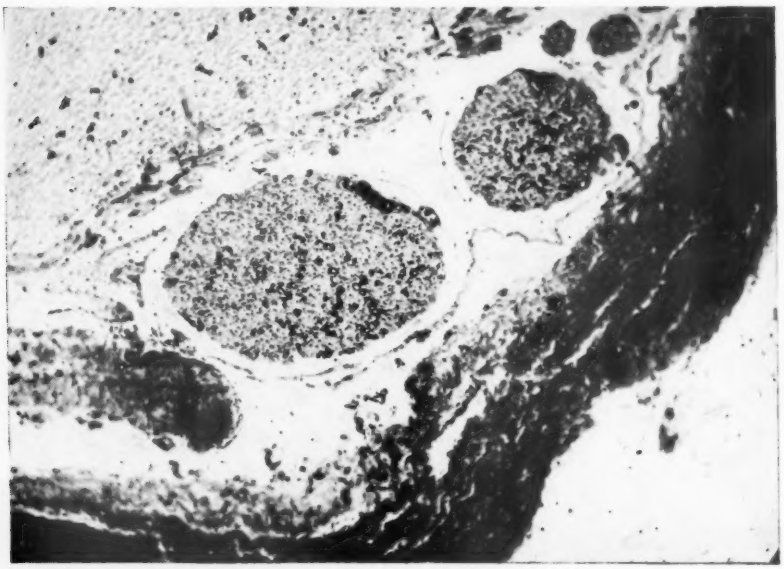

FIG. 7. Transverse section of roots of spinal nerves, showing pia, arachnoid and dura mater, in cervical region. Stained van Gieson (× 100).

initial lesion consists of a developmental aplasia of certain muscle groups, followed by secondary developmental defects in the structure of the joints. On these grounds he advanced the name amyoplasia congenita as giving a more correct description of the condition than the names formerly used. D. S. Middleton[4] simultaneously published his histological findings on muscles obtained by biopsy in cases of arthrogryposis, together with remarks on a lethal hereditary deformity in lambs, studied by Millar in the Institute of Animal Genetics in Edinburgh. Middleton suggested that the deformities were due to the failure of certain muscles to develop completely, with a tendency towards early degeneration, and he concluded that the muscular condition was the primary ætiological factor in the production of these deformities. Fraser Roberts[6] on lambs with 'lethal muscle contracture'

has drawn attention to the fact that hydrops amnii is very marked, that all affected lambs die at birth, and that when there are twins it is rare for both to be deformed. He stated that the condition in lambs depends on the homozygous state of an autosomal recessive factor.

In reviewing the present case with its post-mortem findings in the light of already published work, the following points emerge.

The joint changes in the dissected elbow were marked and such as could be accounted for by the fact that flexion had never been performed in utero. Besides the non-development of the full articular surfaces, certain fibrous bands and ligaments which developed round the joint also contributed towards limiting flexion. The removal of the muscles did not result in free flexion of the elbow joint, movement being still restricted. The chief obstacle was the fibrous tissue which replaced the articular cartilage on the upper part of the greater sigmoid notch. As the limitation of movement in each joint was directly proportionate to the amount of atrophy in the group of muscles responsible, it would appear probable that the joint changes are secondary to the muscle defects, and that the muscle degeneration must be due to some hitherto unexplained cause. The elbow joint may be compared with the condition in congenital dislocation of the hip where the acetabulum is not formed, and is filled with fibrous tissue, the head of the femur never having moved inside it. Why is there not some degree of malformation of the joints in cases of Oppenheim's amyotonia congenita? It may be suggested that the muscle aplasia in this condition is distributed uniformly without antagonistic grouping, leaving a flaccid joint, so that there is some voluntary and perhaps also some flail movement in utero.

In the case under consideration the changes in the affected groups of muscles were marked both naked-eye and microscopically. The muscles found to be most reduced in size on dissection showed most degeneration on section. This leads to the question whether the muscles are ætiologically absent, or whether it is an early intra-uterine degenerative process. Comparing the muscles of the infantile myopathies with this case we find that they are not unlike. In Werdnig-Hoffmann and in Oppenheim's diseases[7, 8] the muscle sections show fibrous tissue, fat replacement, and in many cases great reduction in the size of fibres, which may be so atrophied that they appear to be mere chains of nuclei. The picture of the affected muscles in amyoplasia congenita shows similar degenerative changes, though not so severe, and there are considerably fewer small fibres. There seems to be reason from the appearance of the muscles to place amyoplasia congenita in the same class as the infantile myopathies.

In comparing this condition with the lethal condition in the herd of lambs in Edinburgh, several points of difference are to be found. The disease in lambs appears to be a Mendelian characteristic; this has never been shown in this condition in humans. In lambs hydrops amnii is a constant feature; in children there is frequently recorded some amniotic disturbance, either hydramnios or oligamnios, but often there is no history of any such

abnormality. In lambs there are no secondary joint changes, which may be partly due to the presence of hydramnios, allowing of a free flail-like movement in utero. The diaphragm is always affected in lambs, and invariably causes death at birth. No such case has been recorded in infants. The thymus enlargement is a constant feature in lambs: in the present case the thymus was found post mortem to be rather larger than normal, but this had not been observed clinically or by X-rays, and on section the gland appeared normal.

The spinal cord had been kept for some months in formalin before it was examined. The cells in the anterior horn appeared to be normal in size and number, but there was some lack of myelin in both anterior and posterior roots, with a generalized degeneration of nerve fibres. The anterior horn cells were less affected on one side than the other. In Werdnig-Hoffmann and Oppenheim's diseases, poverty of cells in the anterior horns is a constant feature: there is a diminution both in size and number, and also thinness and poor myelination of the anterior roots with signs of degeneration in the horns. From these differences in the spinal cord this case of amyoplasia congenita would not appear to belong to the same class as those of Werdnig-Hoffmann and Oppenheim. The two last mentioned have not yet provided any definite signs of inflammation. These two conditions show the same pathological picture of muscle and cord, but the clinician can distinguish them from one another quite readily; they are both of the flaccid type. Amyoplasia which is of the rigid spastic type, is distinct clinically from these two, and the pathological picture of the cord is different, though the muscles show the same picture of atrophy as is common to the myopathies.

The sections of the cord in the case of amyoplasia showed evidence of inflammation of the meninges. Red blood corpuscles were scattered throughout the sections, the dura mater was thickened and adherent to the skull, the pia mater was vascular, the central canal of the cord was somewhat larger than normal, and the fontanelle wide. Thus we have evidence of a chronic inflammatory condition of the membranes and of a mild degree of hydrocephalus present at some stage in the developing fœtus, although clinically there were no meningeal symptoms at any time during life, nor was there any apparent hydrocephalus. We have then evidence for the conclusion that the cord changes were not secondary to the muscle condition, but that the primary fault lay within the spinal cord. The selection of groups of muscles at the level of the cervical and lumbar enlargements and the non-involvement of all the other muscles seem to confirm the hypothesis of a central origin. The presence of inflammatory changes in the cord, and the absence of myoblasts in the muscles seem to be inconsistent with any theory of abiotrophy[9].

How could this central infection or injury arise, at what stage in the course of development, and why was the most injury done at the level of the VI, VII and VIII cervical segments and also in the lower lumbar region? Goodall[10] says that fœtal abnormalities such as hydrocephaly, meningocele,

spina bifida, anencephaly, are commonly associated with hydramnios, and that they probably arise from a low grade attenuated infection of the amniotic sac. Abortion occurs early if the infection is severe. Taussig[11] reported 32 cases of hydramnios, with 22 per cent. of fœtal deformities, and a mortality of 44 per cent. Krahula[12] reported 72 cases of hydramnios, with 37·5 per cent. of fœtal deformities and a primary mortality of 54 per cent. Necrosis of the amnion is found in oligamnios. Hydramnios and oligamnios have been reported in connection with arthrogryposis sufficiently often to attract attention to the possibility of an early amniotic infection in these cases. In the embryo the amniotic fluid has access to the brain and sub-meningeal spaces until the closing of the neural tube at the fourth and fifth week of embryonic life. If the amniotic infection occurred when the neural canal had closed in all but the cervical and lower lumbar regions, one might get a deformity such as is present in amyoplasia congenita. In Oppenheim's disease such an infection, if present, would occur when the canal is still wholly open. If the infection occurs after the canal is closed the central nervous system escapes the amniotic infection. Werdnig-Hoffmann's disease is not usually observed at birth, but it may be of interest to quote a case recently under the writer's care. The mother spent Christmas day in bed with a sharp attack of influenza, and on the following 25th of August a child was born, in whom no abnormality was observed in the maternity hospital, but who died of Werdnig-Hoffmann's disease five and a half months later. Definite histories of possible sources of infection to the fœtus are not easily obtained, because at the fourth week of pregnancy the mothers have not yet begun to take note of their health. In the case of amyoplasia under consideration no such history could be elicited. It is, however, possible that, after eight pregnancies in close succession, the mother might have been suffering from a mild chronic endometritis without complaining of it. Some information of value might be gained if this question of early infection during intra-uterine life were followed up, and if in these cases a close examination were made into the history of the mother's health during the fourth and fifth weeks of pregnancy.

Summary.

1. In a case of amyoplasia post-mortem evidence is presented to show that the condition of the joints is secondary to that of the muscles.

2. The cord showed definite signs of meningeal inflammation and a slight degree of hydrocephaly.

3. The disease is compared with Werdnig-Hoffmann's and Oppenheim's diseases.

4. The question of an amniotic infection at the fourth and fifth weeks of intra-uterine life is considered.

My thanks are due to the following who have assisted in the preparation of this communication:—Dr. A. R. Halpenny for performing the

autopsy, and for preparing the sections of the muscles and organs; Dr. C. P. Martin, University Anatomist, and Mr. McEntee, of the School of Anatomy, Trinity College, for the dissection of the arm; Mr. Middleton for examining the muscle sections and for allowing me to examine sections of lamb muscle; Dr. R. J. Gladstone, of King's College, London, for preparing and reporting on the sections of the spinal cord; Dr. Greenfield for examining the cord and muscle sections; Mr. H. A. T. Fairbank for examining the dissection of the elbow joint; and Dr. W. Sheldon for help and advice.

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THE METABOLISM OF HEALING IN CŒLIAC RICKETS

BY

FINDLAY J. FORD, M.D.

(From the Department of Pædiatrics, Glasgow University, and the Biochemical Laboratory, Royal Hospital for Sick Children, Glasgow).

As long ago as 1908 it was reported[1] that in intestinal infantilism there was serious derangement of the mineral metabolism. A number of investigations of the calcium and phosphorus metabolism of patients with fatty diarrhœa, both adults and children, have been made at intervals since that time. It has been consistently found that the serum calcium tended to be low, and the serum inorganic phosphorus either normal or subnormal. Thus, the blood presents the picture of low calcium rickets[2]. Balance studies have shown that the urinary calcium excretion is much reduced, phosphorus excretion diminished, and the fæcal calcium and phosphorus much increased, both relatively and absolutely[3-8]. The data in the literature thus suggest that the bone deformities are due to processes similar to those producing infantile rickets. Parsons[2] in 1927 stated that the bone deformities of cœliac infantilism are rachitic in nature, and that although the blood phosphorus is low, the rickets is of the low calcium type. These conclusions were based on the clinical picture, blood analysis, radiography, and the results of treatment by ultra-violet light or vitamin D.

Gerstenberger and his co-workers[9], on the other hand, suggested that their conception of the production of primary ' low calcium rickets ' does not fit in with the low calcium or combined low calcium low phosphorus types seen in association with cœliac disease. Parsons[10], however, in a later review maintained his former contention, stating that he could see no reason why there should be any distinction between the pathogenesis of the ordinary rickets of infancy and that of cœliac rickets.

In view of this hesitancy to accept cœliac rickets and the ordinary rickets of young children as the same disease in different circumstances, it seemed worth while to record the metabolic observations in the active and healing stages of cœliac rickets, and to compare the results with the changes known to occur in the healing of the infantile type of the disease.

Two patients, girls of six and eight years respectively, presenting the history and clinical characteristics typical of cœliac disease, were found to have active rickets. This was decided on the radiological appearances. In each case the mineral metabolism was studied during this ' active ' period. One child (Case 1) was then given radiostol, one tablet, thrice daily; the other (Case 2) adexolin, one capsule, thrice daily; and the metabolic observa-

tions were repeated after treatment, for two weeks (Case 1) and four weeks (Case 2). Each test period lasted for six or seven days. The diet consisted of whole milk with added sugar; the daily ration was kept constant throughout the periods of study and the intervening period of treatment. The choice of diet, unskimmed milk, was justifiable in view of the fact that neither child had diarrhœa at the time. The intake of minerals could be accurately estimated and was ample to meet the children's requirements.

The radiograms showed, in each patient, well marked rachitic change at the beginning of the study. In Case 1, to whom radiostol had been given for only two weeks, the second plate showed little evidence of healing at the time of the second balance period, but a week later there were radiological signs of commencing improvement. In Case 2 the second plate, taken at the time of the second period, showed advanced healing. This child was treated with adexolin.

In each case the percentage fat retention was extremely poor prior to treatment (Table 1). In Case 1, which showed very early healing, it had risen but was still subnormal on the second observation; but in Case 2 it had returned to the normal level.

TABLE 1.

FAT ANALYSIS IN GRM. PER DAY.

	Intake	Fæcal fat				Retention	
		Neutral	Free fatty acid	Combined fatty acid	Total	Total	Percentage
Case 1.							
1	52·03	2·46	3·38	11·63	17·47	34·56	66·4
2	61·41	1·16	2·37	5·06	8·59	52·72	85·8
Case 2.							
1	44·6	0·97	4·27	4·86	10·1	34·5	77·3
2	42·77	0·13	0·09	0·76	0·98	41·79	97·7

Tables 2 and 3 show the figures for the calcium and phosphorus analysis. There was little change in the urinary calcium but definite increase in the

TABLE 2.

URINARY ANALYSIS: DAILY AMOUNTS.

	CaO		P_2O_5		In c.cm. N/10		Volume in c.cm.
	Output in grm.	As % of intake	Output in grm.	As % of intake	Ammonia	Acidity	
Case 1.							
1	·037	1·42	1·687	45	353·4	239	917
2	·021	0·8	1·906	54·2	394·2	305	830
Case 2.							
1	·052	2·6	0·884	33·2	253·3	31·9	730
2	·043	2·06	1·286	45	148	196·2	670

urinary phosphorus excretion. In Case 2 the urinary ammonia had fallen, and in both Cases 1 and 2 the urinary acidity had increased. All these conform to the findings obtained in the healing of infantile rickets.

Again in the fæces there was great reduction of the output of both CaO and P_2O_5 during healing. In Case 2, in which healing was more advanced, the reduction was so great that the fæcal content of calcium and phosphorus was almost negligible. This is also characteristic of infantile rickets in the healing stage.

TABLE 3.

FÆCAL ANALYSIS: DAILY AMOUNTS.

		CaO		P_2O_5		Fæcal weight	Ash percentage
		Output in grm.	As % of intake	Output in grm.	As % of intake		
Case 1.	1.	2·675	103·5	1·813	48·3	32·4	17·08
	2.	1·244	47·6	0·58	16·4	17·53	13·54
Case 2.	1.	1·843	91·4	1·67	62·9	16·7	26·2
	2.	0·13	6·2	0·04	1·4	1·73	14·6

Table 4 summarizes the results. It will be seen that during the ' active ' period there was either a negative or an extremely small positive balance, whilst during the ' healing ' the retentions were higher than normal figures for children of six and eight years . A similar high level is found in healing rickets.

TABLE 4.

DAILY RETENTION OF CaO AND P_2O_5 IN GRM.

		CaO			P_2O_5		
		Total intake	Total output	Retention per kilo	Total intake	Total output	Retention per kilo
Case 1.	1.	2·58	2·71	−·009	3·75	3·5	+·017
	2.	2·61	1·27	+·092	3·52	2·48	+·072
Case 2.	1.	2·01	1·9	+·008	2·66	2·56	+·007
	2.	2·08	0·17	+·161	2·86	1·33	+·129

In Table 5 are given a series of observations for comparison with the figures for cœliac rickets already detailed. In each type of case, infantile, late and cœliac rickets, the alterations in the retention figures, fæcal output

and urinary phosphorus output, are very similar. Neither the cases of late rickets of unknown ætiology, nor those with cœliac rickets, show the rise in urinary calcium excretion which appears in the infantile cases. This fact was commented on by Stearns, Oelke and Boyd[11] in their paper on the mineral metabolism of late rickets. With this exception the changes are identical.

TABLE 5.

COMPARATIVE TABLE: EXPRESSED IN GRM. PER DAY.

	Rickets	Retention per kgrm.		CaO output		P_2O_5 output	
		CaO	P_2O_5	Urine	Fæces	Urine	Fæces
Infantile rickets. ♂ æt. 10 months	Active	+·037	+·03	·02	1·27	·803	1·003
	Healing	+·07	+·066	·044	0·964	·91	0·59
Late rickets ♂ æt. 9 years	Active	—·003	+·002	·01	2·47	1·5	1·71
	Healing	+·1	+·08	·015	0·38	1·43	0·26
Normal ♂ æt. 10 years		+·033	+·029	·25	1·82	1·6	1·37

It seems justifiable to conclude from these figures that,

(1) The increase in retention of CaO and P_2O_5 in the rickets of cœliac disease is, with antirachitic treatment, similar to that found in infantile rickets.

(2) Increase in urinary excretion of P_2O_5, decrease in ammonia and increase in the acidity of the urine during healing is similar in the two diseases.

(3) Marked reduction of fæcal output of CaO and P_2O_5 occurs in both.

(4) In view of these findings, in conjunction with the recognized clinical, radiological and blood chemistry changes, there is little room for doubt that the rickets of cœliac disease is of the same nature as ordinary infantile rickets.

I desire to thank Professor G. B. Fleming, in whose wards the observations were made, and Dr. N. Morris for suggesting this investigation and for their helpful criticism. I am indebted to Dr. O. Macrae for some of the analytical results.

Appendix.

Summary of case reports.

Case 1.—M. R., girl, aged 8 years. Since 1 year old had large abdomen and had been poorly nourished. Was treated as case of tuberculous peritonitis from age of two years. Never had diarrhœa.

Examination showed large abdomen, flattened buttocks, dry skin, and enlargement of epiphyses. Height 101 cm. (expected height 126 cm.). Weight 15·4 kgrm. (expected weight 26 kgrm.).

Admitted 23.1.31. X-ray of wrists 15.1.31 ' late rickets.' First metabolism period 31.1.31 to 7.2.31. X-ray four days later showed no healing. Radiostol, 1 tablet t.i.d., commenced on 16.2.31 and second metabolism period began on 27.2.31, continued until 6.3.31. X-ray of 4.3.31 ' late rickets,? healing.'

Case 2.—E. A., girl, aged 6 years. Had been treated for cœliac disease for 3½ years.

Examination showed genu valgum, rosary, and enlarged epiphyses. Height 92 cm. (expected height 110 cm.). Weight 13·68 kgrm. (expected weight 19·87 kgrm.).

Admitted on 23.3.31. X-ray 24.3.31 ' late rickets.' First metabolism period 21.4.31, after series of X-rays showed that healing was not taking place spontaneously. Adexolin, 1 capsule t.i.d., commenced on 27.4.31 and second metabolism period began on 27.5.31. X-ray of 28.5.31 ' rickets healing.'

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BRITISH PÆDIATRIC ASSOCIATION

PROCEEDINGS OF THE SIXTH ANNUAL GENERAL MEETING

The Sixth Annual General Meeting was held at the Old England Lake Hotel, Windermere, on Friday and Saturday, the 5th and 6th May, 1933.

First Session (May 5th, 10 a.m.)

Business Proceedings : The President, Dr. Dingwall Fordyce (Liverpool), was in the Chair, and there were present 45 members.

The minutes of the last meeting were read and approved.

The following Officers, Honorary and Ordinary Members were elected.

President : 1933-34, Dr. Eric Pritchard (London).

Secretary : Dr. Donald Paterson (re-elected).

Treasurer : Dr. Morley Fletcher (re-elected).

Representative for Ireland : Dr. F. M. B. Allen in place of Dr. Brian Crichton (resigned).

Representatives for London : Dr. Alan Moncrieff and Dr. A. E. Maitland-Jones.

Honorary Members : Dr. H. Morley Fletcher, Dr. Robert Hutchison and Dr. F. John Poynton (all Past Presidents).

Ordinary Members : Dr. G. W. Bray, of London, Dr. R. W. B. Ellis, of London, Dr. W. F. Gaisford, of Liverpool, Dr. J. V. C. Braithwaite, of Leicester, and Dr. F. J. Ford, of Glasgow.

Next Meeting : The selection of the next place of meeting was left to the Executive Committee.

The Treasurer's report was received and adopted.

Dr. Morley Fletcher asked for the approval of the meeting to the suggestion by the Executive Committee that a sum not exceeding £50 should be utilized for the purpose of the Third International Pædiatric Congress. The meeting approved this.

Dr. Alan Moncrieff suggested that, in view of the recent persecution of the Jewish pædiatricians in Germany that members should, as far as possible, find temporary posts for some of them in this country until things became more settled there.

1. Dr. D. Nabarro (London): 'The incidence of congenital syphilis.' He said that it was impossible to form an accurate estimate of the incidence of congenital syphilis amongst the general population. There is no doubt that race plays a part. For example, in the United states the disease is more prevalent amongst negroes than amongst whites; and probably the world over, the disease is much more prevalent amongst the hospital class than amongst those of a higher social status. Figures varying between 0·6 and 10 per cent., or more, have been given by different observers, for the incidence of congenital syphilis amongst hospital patients. During

the 17 years 1916-32 the author had studied 737 cases, including 32 parents. The average number of cases seen per year is 43, so that the disease can hardly be regarded as negligible. Undoubtedly more cases would be detected by a wider application of the Wassermann and flocculation tests. He was of opinion that untreated congenital syphilis, more particularly in a woman, may be transmitted to the offspring (' third generation syphilis ').

2. Dr. A. V. Neale (Birmingham): ' Some observations on 300 fatal cases of tuberculosis in children.' Observations on the exact necropsy findings in 300 fatal cases of tuberculosis in infants and young children were reported. Practically all had died of miliary tuberculosis and tuberculous meningitis. Detection of the primary route of infection was determined by careful search for the primary focus—intra-thoracic (Ghon tubercles and hilar glands) or abdominal (alimentary). The results were:—(a) primary thoracic (aerogenous infection) 215 or 71·6 per cent., (b) primary abdominal (ingestion infection) 46 or 15·3 per cent.; and (c) no primary focus detectable 39 or 13·0 per cent. In the last group, although no primary focus could be detected, it was almost certain that there had been a rapid generalization after ærogenous infection. In cases under 3 years of age, the numbers in the three groups were 141, 30 and 33 respectively.

66 fatal cases in breast-fed babies under nine months of age, showed that 64 had been initially infected by inhalation on contact with open tuberculosis in an adult—usually parental or in the family circle. Contacts had been traced in many of these cases and a predominance of tuberculous fathers was found. The extreme danger to a baby of exposure to tuberculous adults was emphasized.

3. Dr. C. McNeil (Edinburgh): ' Pyo-pneumothorax.' He said that pyo-pneumothorax, although rarely mentioned in text-books and periodical literature, was not a rare condition. It was nearly always the result of perforation of the pleuræ with the formation of a broncho-pleural fistula. It occurred under various pathological conditions:—in multiple sub-pleural abscesses; in bronchiectasis; in encysted or interlobar empyema, and after surgical operations for empyema; as a result of chronic sub-pleural focal lesions of the lung; and in pulmonary tuberculosis. Where there was a large amount of air in the pleura its clinical recognition was easy, but in the majority of cases the amount of air was small and in those cases it easily escaped recognition. It was frequently associated with staphylococcal or mixed infections of the pleura. Where the lesion in the lung was not serious or extensive prognosis in pyo-pneumothorax was at least no worse than in simple empyema, and in many cases was better.

4. Dr. L. Thatcher (Edinburgh): ' Intra-peritoneal therapy.' He regarded the following as the essential points to be observed for the safe administration of fluids into the peritoneal sac—(1) The nature of the fluid used; 6 per cent. solution of glucose in normal saline is the most satisfactory. (2) This fluid must be injected slowly, at least 45 minutes for the volume used; this being 6-7 ounces as a general rule. (3) The fluid must be kept at or about body temperature all the time; a simple apparatus for maintaining it during the process of administration was described. Charts were shown to demonstrate the value of this therapy in the starvation of acute congenital hypertrophy of the pylorus; in acute infections of the alimentary tract; and in severe dyspepsia, especially that associated with intolerance for carbohydrates.

5. Dr. J. C. Spence (Newcastle): ' Familial periodic paralysis.' Dr. Spence described cases of familial periodic paralysis in a family of which four successive generations had been affected. At the ages of 3 or 4 the affected members of the family began first to be liable to the attacks, which diminished in intensity and frequency after adolescence. Investigation showed that abstention from food played no part in precipitating the attacks. In many of the cases there was a tendency for the paralysis to appear on a Sunday morning, or on other days when they lay in bed to an unusually late hour. Recognizing this they combated the attacks by

rising immediately on feeling the first sensations of muscular weakness, and by exercising freely. This often resulted in aborting the attack. In its severest form the period of paralysis might be 6 or 8 days, during which time the patients were too weak to sit or turn in bed, and had to be fed.

6. Dr. Eric Pritchard (London): 'The medical treatment of obstetric fractures in the new-born.' Dr. Pritchard exhibited a number of X-ray photographs illustrating the possibility of treating obstetric and other fractures in the new-born without splints, bandages, extension apparatus, or other appliances commonly used by surgeons. Some of the films demonstrated the failure of surgical means to improve the position of the fractured bones. Others showed the astonishing reparative power of unaided nature to reduce deformities and restore the axis and alignment of the bones by throwing out an enormous quantity of provisional callus, and subsequently so moulding it and shaping it that the original form and shape of the bone is ultimately attained. In most unpromising cases, with extensive overlapping and deformity, the bones are restored to their original shape within a few months with no shortening or other evidence of the original fracture.

7. Dr. J. H. Thursfield (London): 'Remarks on splenomegaly.' Dr. Thursfield gave a short communication pleading for the reconsideration of the pathology of splenomegaly, and of the rationale of splenectomy. He pointed out that the original ideas which had prompted the advocacy of splenectomy in such diseases as acholuric jaundice and hæmorrhagic purpura had with fuller experience proved to be based on a false pathology, and that especially in the latter disease the doctrine that the removal of the spleen cured the condition by causing a flooding of the circulation with platelets was not wholly in accordance with the facts. All that we were entitled to infer from our experience of splenectomy in a variety of conditions was that the spleen played an important part in the evolution and the well-being of the constituents of the blood, and that in diseased conditions of hæmopoiesis the removal of the organ in diverse circumstances appeared to break a vicious circle. If this view were correct it would be proper to extend the operation of splenectomy to the treatment of other anæmias, and especially to the severer cases of purpura associated with high platelet counts.

8. A. Hayes Smith (Bradford): 'Case of staphylococcal septicæmia in a girl of 10 years with orbital metastasis.' He related an example of this condition due to staphylococcus aureus, secondary to a foruncle on the forearm. Recovery ensued. The treatment comprised concentrated antitoxic antistaphylococcal serum, intramuscular liver liquid, and drainage of the orbit. He considered the absence of eosinophils from the blood picture a valuable sign of septicæmia, their reappearance an indication of improvement. The practical uselessness of blood culture was stressed; and attention was drawn to the early evidence of toxic collapse afforded by the difference between the rectal temperature and that of the dried axilla, a difference of 3° suggesting a guarded prognosis and 5° a very grave one.

At 7 p.m. the Association Dinner took place.

Second Session (May 5th, 8.30 p.m.)

9. Dr. J. C. Spence opened a discussion on 'The prevention of ward infections' and this was followed by some remarks by Doctors Pritchard, Parsons, and Lapage.

10. Dr. K. D. Wilkinson (Birmingham) showed cinematograph pictures of interesting medical cases.

Third Session (May 6th, 10 a.m.).

11. Doctors S. G. Graham and N. Morris (Glasgow): 'The effect of sterilization of milk on the retention of minerals, nitrogen and fat.' Comparisons were made of

the retentions of calcium, phosphorus, fat and nitrogen in each of two healthy infants. The periods were of seven days' duration and the milk throughout came from the same source: prior to and during one period the milk was given raw while before and during the other it was boiled. The retentions of calcium, phosphorus and nitrogen were greater during the boiled milk periods while the retention of fat showed no significant difference on the two types of feeding. It is concluded that during short-term experiments the utilization of minerals, protein and fat is not decreased by sterilization of milk.

12. Dr. A. G. Ogilvie (Newcastle): 'Hereditary hæmorrhagic disease.' The careful and accurate work of Bulloch and Fildes cannot be criticized, but the occurrence of female bleeders and transmission by males deserves further consideration than they gave it. Accumulating reports of inherited purpura with very definite hæmophilic characteristics, together with the occurrence of hæmophilia and bleeding purpura in one and the same family, gives added weight to this view. It is time to extend the restricted view of Bulloch and Fildes, and to take a broader view of the inherited tendency to bleed. Pedigrees illustrating this point abound in the literature, and especially in the monograph of Bulloch and Fildes. Examples of such pedigrees were shown and described.

13. Doctors R. Lightwood and J. C. Hawksley (London): 'Icterus gravis neonatorum.' This condition is coming to be regarded as a clinical sub-variety of erythroblastosis fœtalis, and the group of clinical states with a fœtal erythroblastic background may be classified as follows:—1. Intra-uterine: (a) with universal œdema (=hydrops fœtalis), (b) without œdema; and 2. Neonatal: (c) with severe jaundice and anæmia (=icterus gravis neonatorum), (d) with severe anæmia and little or no jaundice (=anæmia hæmolytica neonatorum).

The grave familial jaundice of the new-born is the most widely recognized of this group of diseases, but icterus gravis is not always familial, isolated cases occurring not infrequently. The main clinical and pathological features of fœtal erythroblastosis are: anæmia, icterus, enlargement of liver and spleen, a large excess of nucleated erythrocytes in the blood, and extensive extra medullary hæmatopoiesis.

An histological study of 12 fatal cases of icterus gravis neonatorium showed important pathological changes in the liver, spleen, kidney, suprarenals, deeper layers of the skin, bone-marrow and brain. In the main the findings confirmed those reported by Clifford and Hertig, and by Blackfan and Diamond, with some additional observations: a sequence of pathological changes was traced in the livers of subjects dying at varying periods after birth. The importance of destructive hepatic changes and the origin of hepatic fibrosis was demonstrated. Icterus gravis neonatorum, by virtue of the selective staining of the basal nuclei, occurring in a small proportion of cases (kernicterus), and by virtue of the hepatic changes now demonstrated may prove to be the common ætiological basis for the hepato-leuticular degeneration of Wilson and the pseudo-sclerosis of Westphal. The possible causal relation of fœtal erythroblastosis with some cases of idiopathic juvenile cirrhosis, splenic anæmia, and anæmias of the von Jaksch's type require investigation.

The following changes in the blood were noted in cases under personal observation:—1. Severe hæmolysis, with marked regenerative activity of erythron. 2. All types of immature erythrocyte occur, with high reticulocytosis. 3. If hæmolysis stops recovery from anæmia ensues; the colour index remains high. 4. Subsidiary changes occur in the white cells and thrombocytes. 5. The mean diameter of the erythrocytes, at first increased, diminishes more rapidly than in normal or premature infants.

Icterus gravis neonatorum has a high mortality rate and a high incidence of sequelæ, particularly from damage to the brain. Repeated transfusions of whole-blood (50 to 70 c.c.) has been the most effective treatment. The transfusions do not appear to arrest hæmolysis but rather to tide the infant over a period of severe anæmia until the hæmolytic process ceases spontaneously.

14. Dr. F. M. B. Allen (Belfast): 'Toxic polyneuritis in two brothers.' He said that the ages of the two brothers were 10 and 12 years, and the children were noticed to be drowsy and heavy six weeks before admission to hospital and four weeks later were staggering. There was gradual loss of power of the limbs, and one complained of sensation of pins and needles. Temperature was normal, the deep reflexes absent, superficial present. Cranial nerves normal, no other ocular changes. Wassermann and Mantoux negative. C.S.F. normal. No evidence of post-diphtheritic infection or poisoning by chemicals. Complete recovery ensued in both cases.

15. Dr. George Bray (London): 'The symtomatology of migraine in childhood.' In studying 100 cases (males 56, females 44) he had found that the first symptom noticed was—vomiting attacks in 33, fits in 2, feverish attacks in 10, abdominal pain in 7, headaches in 39, fainting turns in 5, and eye trouble in 4. In 12 of the cases the first symptom had appeared during the third year, in 2 during the fourth, in 19 during the fifth, and in 16 during the sixth. 76 cases complained of headache (bilateral 58 per cent., unilateral 42 per cent.), 62 of nausea or vomiting, 60 of constipation, 44 of fever, 18 of abdominal pain, 16 of fainting, 10 of dizziness, 9 of eye trouble. Some other allergic manifestation was present in 56 cases. In 82 per cent. of families there were other members showing allergic symptoms, in 60 per cent. unilateral, in 18 per cent. bilateral. Skin tests were positive in 78:—inhalants 25, foods 60 (pork 33, milk 19, beef 11, egg 6, wheat, potato, beans and peas, cocoa, fish 2, banana, tomato, oats 1). A fractional test meal showed achlorhydria in 11 and hypochlorhydria in 59. In cases with migraine alone the white blood count showed 165 eosinophils per c.cm. (1·5 per cent), whilst in cases with other allergic manifestation there were 700 (5 per cent.). In practically all cases the fasting blood sugar was normal.

16. Dr. N. B. Capon (Liverpool): 'Nervousness in childhood.' Dr. Capon gave a communication based upon a series of nervous children seen in private practice and emphasized the importance of studying the child as a whole. He pointed out that insufficient attention seemed to be paid to the mental, intellectual and spiritual aspects of childhood; pædiatric physicians held a privileged position which should enable them to take a broad view. Careful physical examination must come first, and this should include accurate determination of minor defects in sense organs. The key to the trouble was frequently found, however, when the child's environment was investigated, and the pædiatric physician should have valuable observations to make upon important social problems such as birth control, parental discord, divorce, educational methods and so forth.

17. Dr. F. J. Ford (Glasgow): 'The metabolism of healing rickets in cœliac disease.' This communication is published in the present number of the 'Archives of Disease in Childhood.'

18. Dr. J. D'Ewart (Manchester): 'The treatment of rhinitis due to the Klebs-Loeffler bacillus.' Dr. D'Ewart reported thirty-one cases of nasal virulent K.L.B. treated by a weekly X-ray dose of one-third pastille. An aurist reported few cases as clinical diphtheria, several showed inflammatory conditions. The majority gave no ocular evidence. Twelve patients were cured by one treatment, nine by two. Three required six, and one eight. Where discharge was present X-ray cleared it speedily. Attention was drawn to the variation in obtaining negative swabs at weekly intervals. Even after five or six negatives further positives were obtained. It was suggested the K.L.B. persisted in the accessory sinuses. Only three references to X-ray treatment could be found in the literature.